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Semaglutide reverses the chronic myopathy of hyperkalemic periodic paralysis: a case report

Kenneth Brand[1*], Daniel Landry[1], Jeffrey Mulhern[1] and Gregory Braden[1]

Abstract

Background Hyperkalemic Periodic Paralysis (hyperPP) is an autosomal dominant genetic disorder where high extracellular potassium is associated with skeletal muscle depolarization and both flaccid muscle weakness as well as delayed muscle relaxation that can lead to myotonia and myopathy. Interventions have typically relied on avoidance of triggers, low potassium diets, and diuretics like acetazolamide and diclofenamide with limited success.

Case presentation The patient is a 48 year old man with hyperPP from a familial autosomal dominant sodium channel point mutation in the *SCN4A* gene at position 704 with a Threonine to Methionine substitution that lead to symptoms starting in early childhood. By age 30 he developed permanent muscle weakness and neither acetazolamide nor diclofenamide as interventions had improved his myopathy. In the spring of 2023, semaglutide was initiated for weight loss. Before the semaglutide he could not rise out of a chair without help and his gait was very slow. Over the next year his strength and quality of life returned to levels he had not had in decades.

Conclusion This is a promising alternative treatment for hyperPP. By directly acting on skeletal muscle both dependent and independent of insulin, Semaglutide and likely other Glucagon-like peptide agonists show promise as a novel once weekly option that may treat not just the hyperkalemic periodic paralysis but also the skeletal muscle atrophy in a multimodal way.

Keywords Hyperkalemia, Paralysis, Semaglutide, GLP-1, Reversal

Introduction

Glucagon-like Peptide-1s (GLP-1s) like Semaglutide were originally used primarily for blood glucose management in Type 2 Diabetes Mellitus but have since found other niches. Hyperkalemic Periodic Paralysis (hyperPP) is a genetic disorder where high extracellular potassium leads to a more depolarized resting membrane potential in muscle, flaccid paralysis, and myotonia that can eventually lead to myopathy [1]. GLP-1s inhibit glucagon release, enhance the growth of pancreatic beta cells, and increase the production of insulin, which decreases extracellular potassium [2]. Although treatment for hyperPP has relied on therapies targeted to dietary modification, thiazide diuretics, and carbonic anhydrase inhibitors, we report a case of severe symptomatic hyperkalemic periodic paralysis chronic myopathy improved by semaglutide.

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Table 1 Varying strength tests as well as BMI and weight pre and post semaglutide

MSPPBPS	Pre treatment	4 months	7 months	12 months
Standard Gait Test for 3 Meters (seconds / total score)	10.1/0	4.25/3	2.87/4	3.52/4
Fast Gait Test for 3 Meters (seconds / total score)	6.8/0	3.0/4	1.8/4	3.25/4
Repeat Chair Stand Test (seconds/ # / total score)	0/0/0	25.1/5/1	15.4/5/2	20.5/5/1
Total Score	0	12	14	13
Motor Strength Upper Arms	4/5	5/5	5/5	5/5
Motor Strength Upper Legs	4/5	5/5	5/5	5/5
Weight (lbs)	261.8	233.6	221	210
BMI	36.5	33.2	31.3	29.2

Case report

A 48 year old male with hyperPP had the onset of episodic leg weakness at age 4 induced by cold exposure, fasting, and the rest period after exercise. During these episodes of weakness his serum potassium would rise to 5.2–5.7 mEq/L. He would have at least 1 attack per week but after reaching puberty they lessened in frequency. However, the accompanying weakness would last 24 h. His father, uncle, sister, as well as 3 of the 4 sons had an autosomal dominant sodium channel point mutation in the *SCN4A* gene at position 704 with methionine replacing threonine. He had taken acetazolamide 250 mg as well as diclofenamide 100 mg twice daily without much success. By age 30 he developed permanent muscle weakness with no improvement in his myopathy. After 6 years of interventions with acetazolamide and diclofenamide he was having 3 attacks per week lasting two to four hours each.

In the spring of 2023 he was found to have sleep apnea, a weight of 262 pounds, and a body mass index of 36 kg/m^2. Despite an A1c less than 6 and no history of prediabetes, semaglutide 0.25 mg subcutaneously weekly was initiated purely for weight loss and after the third dose he noted less weakness. Before the semaglutide he could not rise out of a chair without help and his gait was very slow. All this weakness improved once the dose of semaglutide reached 1 mg subcutaneously weekly. The dose was then increased to 2.4 mg a week but this caused gastrointestinal issues, so he went back to 1.7 mg every week, where he continues today without the most common side effects from GLP-1 therapy (nausea, vomiting). His attacks have decreased in frequency to once per week now.

Prior to initiating therapy, testing with a Modified Short Physical Performance Battery Protocol and Score sheet (MSPPBPS) was done, to be compared after treatment and determine the effectiveness of the medication at 4, 7, and 12 months (Table 1). The results are consistent with notable improvement in all tests prior to and after initiating therapy. He notes a remarkable improvement in functional status, consistent with the test results.

Discussion

Hypokalemic Periodic Paralysis was first described at the turn of the century, with the hyperkalemic variant discovered later [3]. These all began in infancy, and were often triggered by rest after exercise in addition to fasting [4]. In these cases, the attack frequency would diminish as patients reached their early twenties. However by their 40s, notable proximal limb weakness was identified and many had a permanent myopathy with myofibrillar degeneration noted on biopsies [4]. Early treatments were just as they are today, with thiazide diuretics as well as carbonic anhydrase inhibitors [5].

Mutations to *SCN4a*, a voltage gated sodium channel on the long arm of chromosome 17 (Fig. 1), affect the

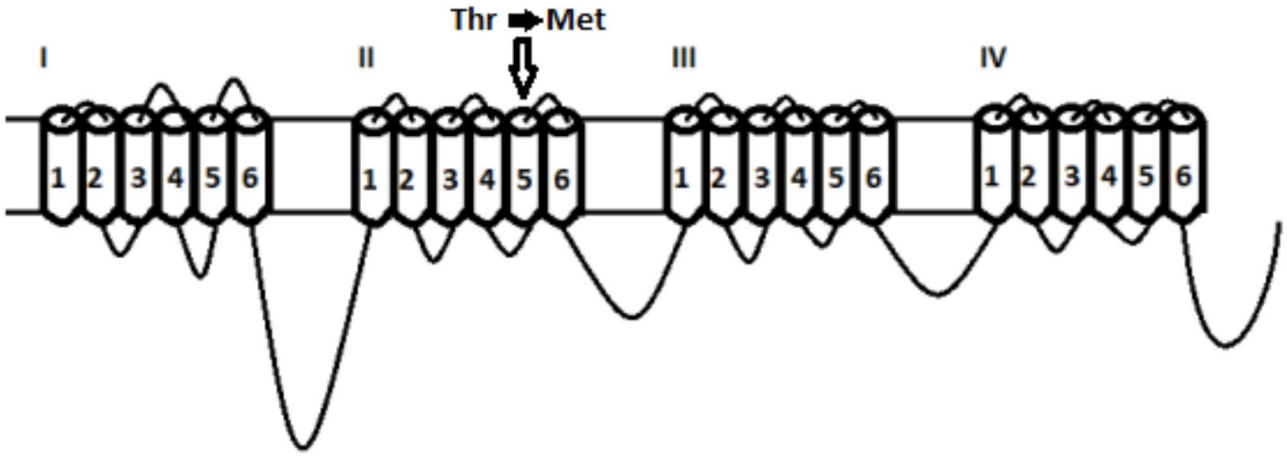

Fig. 1 The *SCN4a* channel mutation

alpha subunit of the sodium channel's fast inactivation gate leading to sustained sodium conductance and often with it myotonia [6–8]. The continued inward sodium current causing membrane depolarization leads to inexcitability and weakness/paralysis [9]. Although hyperkalemia leading to paralysis versus being a consequence of it is still unresolved, hyperkalemia decreases the threshold for neuromuscular depolarization and may precipitate the effects of improper sodium channel conductance [10]. The most common mutation is threonine to methionine (shared by this patient) in one of the transmembrane domain's alpha subunits [6].

Semaglutide is a GLP-1 targeting GLP-1 receptors found throughout the body. GLP-1s inhibit glucagon release, enhance the growth of pancreatic beta cells, and increase the production of insulin [7–9]. Besides their insulinotropic role, some murine and human studies have shown the benefit of GLP-1s in possibly reversing myopathy by promoting skeletal muscle growth and decreasing skeletal muscle atrophy [10, 11]. Although the kidneys have the predominant role in potassium balance, skeletal muscle contains 80% of intracellular potassium, which insulin tightly regulates via increasing Na/K pumps [12]. This is achieved by insulin's activation of the alpha-2 subunit present in both muscle cells and adipocytes. Insulin also induces hyperpolarization of the cell membrane, in contrast to hyperkalemia, where it is depolarized [13].

GLP agonists have carved a niche with their ability to promote weight loss [14]. Although many of the improved MSPPBPS findings could be explained by reduction in weight, like the Standard and Fast Gait tests, the decrease in attacks of flaccid weakness associated with hyperPP points against weight loss as the only mechanism for his improvement. Likely, the multimodal mechanisms of GLP-1s help prevent the onset of attacks, as discussed herein.

GLP-1s promote an increase in insulin gene synthesis in Beta Cells. It does this by upregulating the WNT family Member 5 A (WNT5a) class of proteins that promote beta cell proliferation [7]. Newly diagnosed diabetics have markedly decreased levels of WNT5a, which mirrors known diabetic physiology [15]. With GLP-1 exposure there are increased levels of WNT5a leading to a Beta cell increase, an increase in insulin secretion, and an increase in intracellular potassium storage, diminishing hyperkalemia [8, 9].

GLP-1s also promote beta cell longevity, which further allows them to decrease hyperkalemia by effective insulin release [8]. GLP-s decrease beta cell endoplasmic reticulum stress via activation of glutathione peroxidase and other mediators promoting β cell proliferation and inhibiting β cell apoptosis [8]. This net effect serves to counter hyperkalemia via Insulin's effect on Na/K pumps.

GLP-1s directly act on skeletal muscle microenvironment to increase insulin sensitivity. GLP-1 receptor abundance on endothelial surfaces allows GLP-1s to relax the endothelium via AMPK phosphorylation and increase microvascular recruitment as well as muscle capillary density [16]. This acts to increase nutrient flow to the muscle, including insulin, which amplifies insulin sensitivity [17].

GLP-1s switch muscle fiber type to promote insulin sensitivity. GLP-1s induce fast twitch (glycolytic and insulin resistant) to slow twitch (oxidative and insulin sensitive) fiber changes [18]. This was experimentally verified in C2C12 myotubules, a mouse myoblast cell line with diminished insulin sensitivity [18].

Besides their pro-insulin and muscle fiber switching effects, GLP-1s also affect skeletal muscle proliferation and serve to increase the reservoir for intracellular potassium uptake. The gastrocnemius of mice treated with semaglutide show an increase in muscle mass, an increase in the ratio of type 1 to typer 2 muscle fibers, muscle fiber area and density, sarcomere length, as well as mitochondrial number and area [18]. These effects have been tested and confirmed predominantly in obese settings, which may explain the success our patient had. By increasing skeletal muscle synthesis as well as the proportion of type 1 skeletal muscle, this augment's the body's ability to store potassium intracellularly.

Maintenance of skeletal muscle hypertrophy and hyperplasia, and therefore intracellular potassium storage, are due to GLP-1s effect on myostatin feedback and their prevention of myotubular necroptosis. Myostatin regulates both muscle fiber, number, and size and its pathway is highly conserved in muscle atrophy [10]. GLP-1 agonists decrease myostatin expression via protein kinase A and B signaling pathways not only in dexamethasone-induced but also CKD-induced muscle atrophy [10]. GLP-1s also suppress muscle inflammation by inhibiting necroptosis, a programmed lytic cell death. Agonism of the GLP-1 receptor in inflammatory skeletal muscle myopathies suppresses myotubular necroptosis via downregulating PGAM5 as well as suppressing Reactive Oxygen Species [10].

HyperPP is an inherited autosomal dominant disorder of skeletal muscle sodium channels that leads to elevated serum potassium and muscle hyperexcitability from the increased intracellular resting membrane potential and leads to progressive myopathy. By altering insulin signaling as well as skeletal muscle physiology, semaglutide increases intracellular storage of potassium and decreases the symptoms and associated myopathy in hyperPP. Though more cases and objective measures of muscle mass would be necessary to help confirm the causal relationship, semaglutide and likely other Glucagon-like peptide agonists show promise as a novel once

weekly option that may treat not only the hyperkalemic periodic paralysis but also the skeletal muscle atrophy in a multimodal way.

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Data availability
Image data for Fig. 1 was created by the corresponding authors and is available at https://fairsharing.org/6163. The data in Table 1 is collected from the patient and is not from any dataset or repository to protect patient privacy.

Declarations

Ethics approval and consent to participate
Written Informed Consent for the clinical details was obtained by the participant prior to writing of the paper in accordance with the Baystate ethics principals.

Consent for publication
Written Informed consent for the clinical details was obtained by all participants prior to writing of the paper in accordance with the Baystate ethics principals.

Competing interests
The authors declare no competing interests.

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References

1. Fontaine B, Lapie P, Plassart E, et al. Periodic paralysis and voltage-gated ion channels. Kidney Int. 1996;49(1):9–18. https://doi.org/10.1038/ki.1996.2.
2. Smith NK, Hackett TA, Galli A, Flynn CR. GLP-1: Molecular mechanisms and outcomes of a complex signaling system. Neurochem Int. 2019;128:94–105. https://doi.org/10.1016/j.neuint.2019.04.010.
3. Myopathy of Hypokalemic Periodic Paralysis: An Electron Microscopic Study | JAMA Neurology | JAMA Network. Accessed 4 Apr, 2024. https://jamanetwork.com/journals/jamaneurology/article-abstract/568933
4. Progressive Myopathy in Hyperkalemic Periodic Paralysis | JAMA Neurology | JAMA Network. Accessed 4 Apr, 2024. https://jamanetwork.com/journals/jamaneurology/article-abstract/590332
5. Sekhon DS, Vaqar S, Gupta V. Hyperkalemic Periodic Paralysis. In: StatPearls. StatPearls Publishing; 2024. Accessed 4 Apr, 2024. http://www.ncbi.nlm.nih.gov/books/NBK564319/
6. Akaba Y, Takahashi S, Sasaki Y, Kajino H. Successful treatment of normokalemic periodic paralysis with hydrochlorothiazide. Brain Dev. 2018;40(9):833–6. https://doi.org/10.1016/j.braindev.2018.05.011.
7. Liu Z, Habener JF. Glucagon-like peptide-1 activation of TCF7L2-dependent Wnt signaling enhances pancreatic beta cell proliferation. J Biol Chem. 2008;283(13):8723–35. https://doi.org/10.1074/jbc.M706105200.
8. Xu W, Sang YQ, Liu XK, et al. Effect of glucagon-like peptide-1 receptor agonist on insulin secretion index and serum Wnt5a protein in patients with new-onset type 2 diabetes mellitus. J Diabetes Metab Disord. 2023;22(1):539–45. https://doi.org/10.1007/s40200-022-01175-0.
9. Chan HM, Jain R, Ahrén B, Pacini G, D'Argenio DZ. Effects of increasing doses of glucagon-like peptide-1 on insulin-releasing phases during intravenous glucose administration in mice. Am J Physiol - Regul Integr Comp Physiol. 2011;300(5):R1126–33. https://doi.org/10.1152/ajpregu.00687.2010.
10. Hong Y, Lee JH, Jeong KW, Choi CS, Jun H. Amelioration of muscle wasting by glucagon-like peptide-1 receptor agonist in muscle atrophy. J Cachexia Sarcopenia Muscle. 2019;10(4):903–18. https://doi.org/10.1002/jcsm.12434.
11. Kamiya M, Mizoguchi F, Yasuda S. Amelioration of inflammatory myopathies by glucagon-like peptide-1 receptor agonist via suppressing muscle fibre necroptosis. J Cachexia Sarcopenia Muscle. 2022;13(4):2118–31. https://doi.org/10.1002/jcsm.13025.
12. Cheng CJ, Kuo E, Huang CL. Extracellular potassium homeostasis: Insights from hypokalemic periodic paralysis. Semin Nephrol. 2013;33(3):237–47. https://doi.org/10.1016/j.semnephrol.2013.04.004.
13. Zierler K, Rogus EM, Scherer RW, Wu FS. Insulin action on membrane potential and glucose uptake: Effects of high potassium. Am J Physiol. 1985;249(1 Pt 1):E17–25. https://doi.org/10.1152/ajpendo.1985.249.1.E17.
14. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989–1002. https://doi.org/10.1056/NEJMoa2032183.
15. Wingless-type. MMTV integration site family member 5a: A novel biomarker regulated in type 2 diabetes mellitus and diabetic kidney disease — King's College London. Accessed 4 Apr, 2024. https://kclpure.kcl.ac.uk/portal/en/publications/wingless-type-mmtv-integration-site-family-member-5a-a-novel-biom
16. Liu J, Liu Z. Muscle insulin resistance and the inflamed microvasculature: Fire from within. Int J Mol Sci. 2019;20(3):562. https://doi.org/10.3390/ijms20030562.
17. Zhao L, Fu Z, Wu J, et al. Globular adiponectin ameliorates metabolic insulin resistance via AMPK-mediated restoration of microvascular insulin responses. J Physiol. 2015;593(Pt 17):4067–79. https://doi.org/10.1113/JP270371.
18. Ren Q, Chen S, Chen X, et al. An effective Glucagon-Like Peptide-1 receptor agonists, semaglutide, improves sarcopenic obesity in obese mice by modulating skeletal muscle metabolism. Drug Des Devel Ther. 2022;16:3723–35. https://doi.org/10.2147/DDDT.S381546.

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