Annals of Case Reports
Boros E, et al. Ann Case Rep: 7: 1062
www.doi.org/10.29011/2574-7754.101062
www.gavinpublishers.com

Case Report

Autosomal Dominant Hypocalcemia Type I: About Difficult Management Despite 1-34 Recombinant PTH Treatment in an Infant

Emese Boros*, Claudine Heinrichs, Cecile Brachet

Pediatric Endocrinology Unit-Hôpital Universitaire de Bruxelles, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Belgium

***Corresponding author**: Emese Boros, Pediatric Endocrinology Unit-Hôpital Universitaire de Bruxelles, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Av J J Crocq 15, 1020 Bruxelles, Belgium

Citation: Boros E, Heinrichs C, Brachet C (2022) Autosomal Dominant Hypocalcemia Type I: About Difficult Management Despite 1-34 Recombinant PTH Treatment in an Infant. Ann Case Report. 7: 1062. DOI: 10.29011/2574-7754.101062

Received Date: 23 November 2022; **Accepted Date**: 28 November 2022; **Published Date**: 30 November 2022

Abstract

Autosomal dominant hypocalcemia type I is due to a gain-of-function mutation in *CASR*. We report on a very symptomatic patient in whom classical treatment lead to massive hypercalciuria, so that recombinant 1-34 PTH was used from 8 weeks of life. Our aim is to document pitfalls of this treatment.

Keywords: Autosomal dominant hypocalcemia; Infant; Recombinant 1-34 PTH; CASR activating mutation; Pump therapy

Abbreviations: CASR: Calcium sensing receptor; ADH: Autosomal dominant hypocalcemia; PTH: Parathormone; NR: Normal range

Introduction

Calcium sensing receptor (CASR) is a G-protein-coupled receptor that plays an essential role in calcium homeostasis. It is expressed mainly in the parathyroid glands, kidneys and bones. It mediates parathormone (PTH) secretion and also directly regulates the rate of divalent cation reabsorption by the kidneys [1, 2, 3]. Heterozygous activating mutations in *CASR* cause Autosomal dominant hypocalcemia (ADH), characterized by hypocalcaemia with inappropriately low PTH levels and high urinary calcium excretion. Additionally, hyperphosphatemia and hypomagnesaemia are present. The clinical manifestations of ADH vary from asymptomatic or mild paresthesia to seizures [4, 5]. Treatment of symptomatic ADH patients is challenging. The risk of nephrocalcinosis is increased by vitamin D analogs, calcium and magnesium supplementation [5]. Subcutaneous recombinant 1-34 PTH as a treatment for hypoparathyroidism in adults was first described in 1996. [6] In 1998, Winer et al reported that adult patients with an activating *CASR* mutation required higher doses of recombinant 1-34 PTH than patients with hypoparathyroidism; the treatment did not normalize but significantly lowered urinary calcium / creatinine ratio [7]. The use of recombinant 1-34 PTH in children with hypoparathyroidism was first described in 2008. [8] In 2011, recombinant 1-34 PTH delivered by an insulin pump [9] was reported to be a good therapeutic alternative since it reduces calciuria. A few patients with long-term follow-up with 1-34 recombinant PTH were published: 13.5 years with twice daily injections [10] and 8 years with pump delivery [11]. PTH delivered by pump seems to produce the most physiological replacement. [12] However, currently, no consensus on ADH treatment exists, especially during infancy.

We report on an infant with ADH treated with recombinant 1-34 PTH from the age of 8 weeks. Our aim is to document the pitfalls encountered during 5.5 years of treatment.

Case Report

A male neonate was referred to our pediatric endocrinology unit for hypocalcaemia. The boy was born at 37 weeks with 4,060 kg (2, 2 SDS), 54 cm (2, 2 SDS), and a head circumference of 37

cm (2, 7 SDS). The pregnancy was obtained after reimplantation of a frozen embryo obtained by *in vitro* fertilization. Polyhydramnios was present during pregnancy. At 37 weeks of gestation, the mother presented a nephritic colic and labor was induced due to maternal renal dilatation. On the first day of life, tremor was observed. Laboratory investigations showed hypoglycemia which was rapidly corrected. Despite normal glycaemia, tremor persisted. Hypocalcemia (calcium 1.57 mmol/l, NR: 2.2-2.7) was noted along with hyperphosphatemia (Phosphore 3.25 mmol /L, NR: 1.28-2.08), hypomagnesiemia, (Magnesium 0, 59 mmol/l, NR: 0.66-1.07) low PTH (PTH 5 ng/l, NR: 15-65) and hypercalciuria (5.470 mol/mol creatinine, NR: <2.200) (Figure 1). A heterozygous de novo activating mutation in *CASR* gene was found (c.374T>C). As he was symptomatic, calcium supplementation and vitamin D analogs were started. The patient also received magnesium supplementation (20 mg/kg/day elemental magnesium), hydrochlorothiazide (1 mg/kg/day) (in order to reduce hypercalciuria) and 800 UI/day of 25 OH vitamin D. Despite treatment, calcemia stayed low and calciuria increased. At 6 weeks of life, the clinical exam revealed an extreme irritability and poor weight gain. Calcemia was 1, 65 mmol/l and calciuria was 5.905 mol/mol creatinine. Consequently, at 8 weeks of life, treatment with recombinant 1-34 PTH was started as a continuous subcutaneous infusion with a Minimed 640 G insulin pump (Medtronic). Classical treatment was stopped. The starting dose was 0.47 µg/ kg/day. 60 mcg (0, 24 ml) recombinant 1-34 recombinant PTH was diluted in 1, 56 ml of 0, 9% saline solution in the 1.8 ml reservoir.

Calcemia normalization occurred within the first 12 hours. Phosphatemia normalized within 7 days. Calciuria significantly dropped within 1 week. The catheter was replaced every 72h. The site of subcutaneous catheter insertion was also modified every 72h. Buttocks, lower back and thighs were used as catheter insertion sites. Both parents got the instructions about management. During febrile episodes, the flow rate was increased to 120%, preceded by a 4U bolus (1.33 µg of recombinant 1-34 PTH).

At 5.5 month of age, 6.5 and 13 months of age, he presented a stridor. At 5.5 month of age, stridor led the parents to consult the emergency department. No infection was present but a severe hypocalcemia of 1.42 mmol/l (reference range 2.25-2.75), hypomagnesemia (0.60 mmol/L (N.R.0.66-1.07)) and hyperphosphatemia (2.89 mmol/L (N.R.1.28-2.08)) were noted. Serum 25 OH vitamin D was 45.8 ng/ml 1 month before. Initially, PTH dose was increased and he received calcium supplementation but calcemia did not improve (stayed at 1.87 mmol/l); the catheter and the site of insertion was replaced without success. Then 50 000 UI of vitamin D were given orally and calcemia increased to reach hypercalcemia after 72 h (3.12 mmol/l) so PTH was reduced to his usual dose.

After this episode, vitamin D was increased to 25 000 UI/week. Throughout the follow-up serum levels of 25 (OH) vitamin D were mostly in the high normal values between 77-95 µg/l One month later, stridor improved after subcutaneous catheter replacement.

At 13-months of age, hypocalcemia re-ocurred, (1.53 mmol/l) despite normal serum 25OH Vitamin D (53 µg/l, NR: 30-80) and catheter replacement. Initially, 1-34 PTH doses were increased but without improvement. Calcemia normalized only after administration of a bolus of 50 000 UI of oral vitamin D.

During follow-up, the dilution of the 1-34 recombinant PTH was changed, adding less saline solution, (0,78 ml saline rather than 1.56 ml leading to a more concentrated PTH solution) and improvement was obtained. He required then 0.75 µg/kg/day of 1-34 recombinant PTH. We do not used pure recombinant 1-34 PTH, in order to reduce waste of product, as the product is expensive. At the same age, we observed that calcemia decreased after 48h of catheter replacement. Consequently, the catheter was replaced every 48h. The dose of the recombinant 1-34 PTH was progressively increased to 0, 7 mcg/kg/day in order to normalize calcemia and reduce hypercalciuria. Also, bubbles were observed in the reservoir and the tube, leading to a drop in calcemia when bubble were present. So, the parents are checking, at least every 8 h, for bubbles in the catether. In 2021 Omnipod Dash became available in Belgium and at 4 years and 3 month he started to use it. Initially the same dose was used, but hypercalcemia was observed and dosage of recombinant 1-34 PTH has been decreased at 0.55 µg/kg/day.

Currently, the patient is 5.7 years old, his development and growth are perfectly normal (Figure 2).

Nephrocalcinosis, first noticed before the recombinant 1-34 PTH treatment, has initially evolved, and at 2,5 years of age a low citrate excretion (172.9 mg/24 h NR: >300) with a high urinary calcium/urinary citrate was found (1.33 mg/mg, considered normal >0.7 (13)). Treatment with potassium citrate was initiated 0.4 mmol of citrate/kg. Since then, no evolution of nephrocalcinosis is seen.

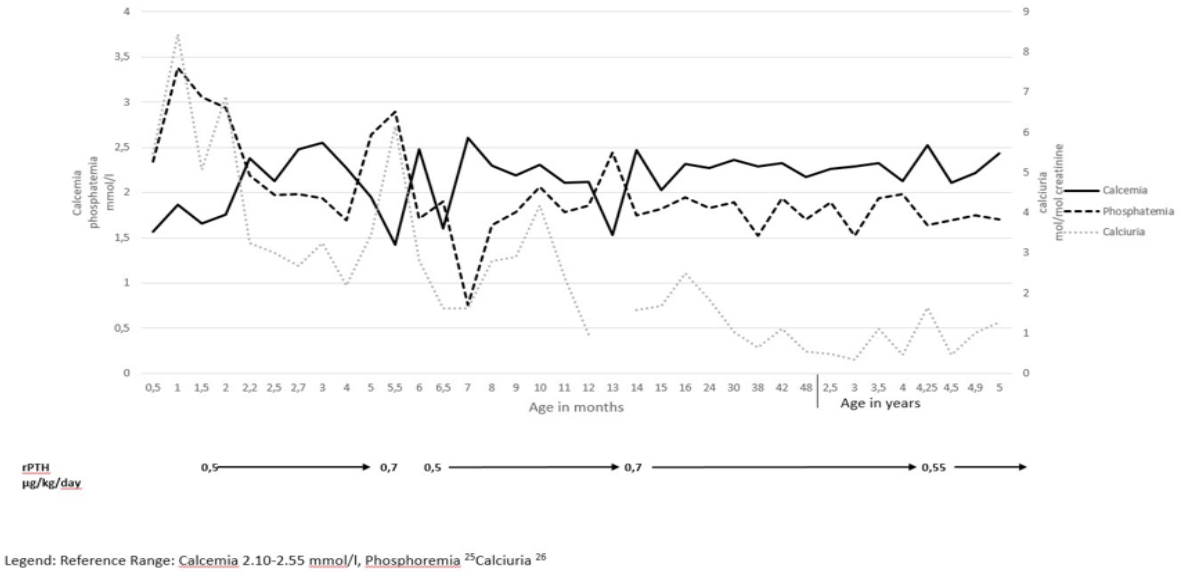

Figure 1: Evolution of calcemia, phosphatemia and calciuria and treatment during the follow up.

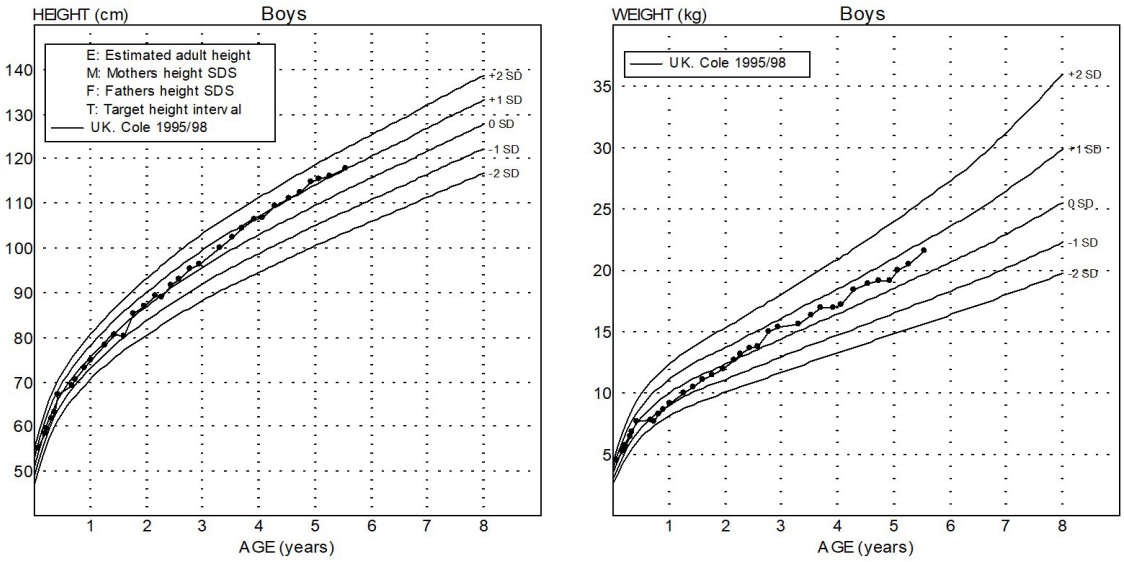

Figure 2: Growth chart of the patient.

Discussion

We report on a young infant with ADH type I treated with continuous 1-34 recombinant PTH delivered by insulin pump. Treatment was started as soon as 8 weeks of life with a follow-up of 5.5 years. During follow-up we encountered several problems. Higher doses of vitamin D were necessary to avoid hypocalcemia. Nephrocalcinosis worsened despite the treatment and despite normalized calciuria; hypocitraturia was observed and once citrate supplements were added, nephrocalcinosis stabilized. Finally bubble formation in the reservoir and tube contributed to the decrease in the serum calcium levels, using a tubeless pump allowed even to reduce the recombinant 1-34 PTH.

Indeed since 1996 a few reports using recombinant 1-34 PTH are published in adults. In 2012, pump delivery permitted a better calcium homeostasis and a dose reduction [14]. Shortly later, 1-34 PTH was used for the first time in children with hypoparathyroidism, and was shown to be superior to calcitriol [15, 16, 17] Using PTH via an insulin pump in children was first described in 2011 by Linglart et al in 2 children with APECED and one with idiopathic hypoparathyroidism. [9] In the neonatal period, PTH treatment was reported by Cho et al for a neonate with HDR syndrome for a period of 12 days [18]. In a recent paper 3 infants started continuous 1-34 recombinant PTH before 12 weeks of age, but the follow up was only 0.8 to 3.6 years. [19] The longest reported follow-up of 1-34 PTH pump delivery is 8 years [11] in a patient with hypoparathyroidism who started 1-34 PTH treatment at 6 years and 2 months of age [10]. Our patient started as soon as 8 weeks of life, and doing well after 5.5 years of treatment.

Higher doses than usual of oral vitamin D were necessary in our patient in order to maintain a normal plasmatic 25OH D level during recombinant 1-34 PTH. Maintaining a normal-high 25 OHD plasma level seemed to help avoiding hypocalcemia. One of our limitations to this affirmation is not having a serum level of 25 OH D at the moment of hypocalcemia at 5.5 months of age. Maintaining normal 25 OH D levels for successful results was already reported [9] in a patient with profound vitamin D deficiency.

We also observed hypocalcemia due to bubble formation in the tube between the pump and the subcutaneous catheter delivering recombinant 1-34 PTH. Bubble formation using PTH has never been reported, but bubble formation is frequently reported by patients using insulin pumps [20, 21]. The use of Omnipod Dash permitted to decrease the recombinant 1-34 PTH dose in our patient to 0.55 µg/kg/day. In ADH the reported doses of 1-34 recombinant PTH continuous infusion are varying between 0.3 to 0.9 µg/kg/day [9, 19].

Maintaining the lowest effective dose of 1-34 recombinant PTH is important, to minimalize potential long term side effects. When administered intermittently, recombinant 1- 34 PTH stimulates bone turnover and increases bone volume, as shown in the iliac biopsies done by Gafni et al in patients with hypoparathyroidism (2 adults and 3 adolescents) treated with 1-34 recombinant PTH for 1 year at a mean dose of 0.57 µg/kg/j administered 2 or 3 times a day by subcutaneous injections. [22] Theman also reported a thickened calvaria after 13, 5 years of treatment with intermittent 1, 34 recombinant PTH. [10] The effects of continuous 1-34 recombinant PTH are different in healthy subject, mostly catabolic [23] but needs further studies in ADH patients.

Hypocitraturia is a known risk factor for developing nephrocalcinosis and nephrolithiasis, and is one of the side effects of the1-34 recombinant PTH treatment in hypoparathyroidism reported by Gafni et al in 2018. [13] In our patient we found that urinary citrate was low after 2.5 years of treatment, and this may contribute to the evolution of the nephrocalcinosis.

In conclusion, we report on long term continuous subcutaneous 1-34 PTH treatment in a symptomatic infant with ADH with extremely high calciuria. Given the failure of the classical treatment to correct calcemia and calciuria, recombinant 1-34 PTH was started as early as 8 weeks of life. This treatment is still ongoing at the age 5.7 years. The patient reported here is among the youngest started on continuous 1-34 recombinant PTH treatment along with the 3 patients reported in 2021 [19] and the treatment improved both hypocalcemia and hypercalciuria. We also observed, as already reported in the literature, that maintaining normal serum levels of 25OH vitamin D is important for good results. Bubble formation in the catheter delivering 1-34 PTH is one of the inconvenient of pump delivery in our patient. The clinical outcome after 5.5 years is excellent. More studies are needed to document long-term safety and assess novel therapeutic options such as calcilytic treatment [24].

Acknowledgements

We would like to thank members of endo-ern for their contribution in discussing the case. We also thank A Linglart from Hôpital Bicêtre in Paris for her precious help in the treatment decisions.

We are grateful to the patient and his parents for their trust in the medical management and the medical team.

Ethics Statement

The parents of the patient have given their written informed consent to publish their case.

Disclosure Statement

The authors have no potential conflicts of interest to declare.

Author Contributions

EB, CB wrote the article. EB was the treating physician. CH critically reviewed the manuscript.

References

1. Thakker RV (2004) Diseases associated with the extracellular calcium-sensing receptor. Cell Calcium; 35: 75-82.
2. Hebert SC, Brown EM, Harris HW (1997) Role of the Ca (2+)-sensing receptor in divalent mineral ion homeostasis. J Exp Biol; 200: 295-302.
3. Brown EM, MacLeod RJ (2001) Extracellular calcium sensing and extracellular calcium signaling. Physiol Rev; 81: 239-97.
4. Brown EM (1997) Mutations in the calcium-sensing receptor and their clinical implications. Horm Res; 48: 199-208.

5. Lienhardt A, Bai M, Lagarde JP, Rigaud M, Zhang Z, et al. (2001) Activating mutations of the calcium-sensing receptor: management of hypocalcemia. J Clin Endocrinol Metab; 86: 5313-23.

6. Winer KK, Yanovski JA, Cutler GB (1996) Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism. JAMA; 276: 631-6.

7. Winer KK, Yanovski JA, Sarani B, Cutler GB (1998) A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1-34 in treatment of hypoparathyroidism. J Clin Endocrinol Metab; 83: 3480-6.

8. Winer KK, Sinaii N, Peterson D, Sainz B, Cutler GB (2008) Effects of Once Versus Twice-Daily Parathyroid Hormone 1–34 Therapy in Children with Hypoparathyroidism. J Clin Endocrinol Metab; 93: 3389-95.

9. Linglart A, Rothenbuhler A, Gueorgieva I, Lucchini P, Silve C, Bougnères P (2011) Long-Term Results of Continuous Subcutaneous Recombinant PTH (1-34) Infusion in Children with Refractory Hypoparathyroidism. J Clin Endocrinol Metab; 96: 3308-12.

10. Theman TA, Collins MT, Dempster DW, Zhou H, Reynolds JC, et al. (2009) PTH(1-34) replacement therapy in a child with hypoparathyroidism caused by a sporadic calcium receptor mutation. J Bone Miner Res Off J Am Soc Bone Miner Res; 24: 964-73.

11. Saraff V, Rothenbuhler A, Högler W, Linglart A (2018) Continuous Subcutaneous Recombinant Parathyroid Hormone (1-34) Infusion in the Management of Childhood Hypoparathyroidism Associated with Malabsorption. Horm Res Paediatr; 89: 271-7.

12. Winer KK (2019) Advances in the treatment of hypoparathyroidism with PTH 1-34. Bone; 120: 535-41.

13. Gafni RI, Langman CB, Guthrie LC, Brillante BA, James R, Yovetich NA, et al. (2018) Hypocitraturia Is an Untoward Side Effect of Synthetic Human Parathyroid Hormone (hPTH) 1-34 Therapy in Hypoparathyroidism That May Increase Renal Morbidity. J Bone Miner Res Off J Am Soc Bone Miner Res; 33: 1741-7.

14. Winer KK, Zhang B, Shrader JA, Peterson D, Smith M, Albert PS, et al. (2012) Synthetic Human Parathyroid Hormone 1-34 Replacement Therapy: A Randomized Crossover Trial Comparing Pump Versus Injections in the Treatment of Chronic Hypoparathyroidism. J Clin Endocrinol Metab; 97: 391-9.

15. Winer KK, Sinaii N, Reynolds J, Peterson D, Dowdy K, Cutler GB (2010) Long-Term Treatment of 12 Children with Chronic Hypoparathyroidism: A Randomized Trial Comparing Synthetic Human Parathyroid Hormone 1-34 versus Calcitriol and Calcium. J Clin Endocrinol Metab; 95: 2680-8.

16. Winer KK, Ko CW, Reynolds JC, Dowdy K, Keil M, Peterson D, et al. (2003) Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. J Clin Endocrinol Metab; 88: 4214-20.

17. Winer KK, Fulton KA, Albert PS, Cutler GB (2014) Effects of pump versus twice-daily injection delivery of synthetic parathyroid hormone 1-34 in children with severe congenital hypoparathyroidism. J Pediatr; 165: 556-563.e1.

18. Cho YH, Tchan M, Roy B, Halliday R, Wilson M, Dutt S, et al. (2012) Recombinant parathyroid hormone therapy for severe neonatal hypoparathyroidism. J Pediatr; 160: 345-8.

19. Sastre A, Valentino K, Hannan FM, Lines KE, Gluck AK, Stevenson M, et al. (2021) PTH Infusion for Seizures in Autosomal Dominant Hypocalcemia Type 1. N Engl J Med; 385: 189-91.

20. Lopez PE, King BR, Goss PW, Chockalingam G (2014) Bubble formation occurs in insulin pumps in response to changes in ambient temperature and atmospheric pressure but not as a result of vibration. BMJ Open Diabetes Res Care; 2.

21. Taleb N, Messier V, Ott-Braschi S, Ardilouze JL, Rabasa-Lhoret R (2018) Perceptions and experiences of adult patients with type 1 diabetes using continuous subcutaneous insulin infusion therapy: Results of an online survey. Diabetes Res Clin Pract; 144: 42-50.

22. Gafni RI, Brahim JS, Andreopoulou P, Bhattacharyya N, Kelly MH, Brillante BA, et al. (2012) Daily parathyroid hormone 1-34 replacement therapy for hypoparathyroidism induces marked changes in bone turnover and structure. J Bone Miner Res Off J Am Soc Bone Miner Res; 27: 1811-20.

23. Estell EG, Rosen CJ (2021) Emerging insights into the comparative effectiveness of anabolic therapies for osteoporosis. Nat Rev Endocrinol; 17: 31-46.

24. Roberts MS, Gafni RI, Brillante B, Guthrie LC, Streit J, et al. (2019) Treatment of Autosomal Dominant Hypocalcemia Type 1 with the Calcilytic NPSP795 (SHP635). J Bone Miner Res Off J Am Soc Bone Miner Res; 39: 1609-1618.

25. Peskovitz O, Eugster E (2004) Bone and mineral metabolism in Pediatric Endocrinology. Mechanism, Manifestations and Management. Philadelphia: Lippincott Williams and Wilkins. 2004

26. Garabedian M, Linglart A, Mallet E, Lienhardt A (2011) Métabolisme phosphocalcique et osseux de l'enfant. 2e edition. Paris: Médecine Sciences Publications.