

Management of Refractory Hypoparathyroidism to conventional treatment

Manejo del hipoparatiroidismo refractario al tratamiento convencional

Evelien Gevers

Consultant Paediatrician in Endocrinology and Diabetes and Honorary Reader in Paediatric Endocrinology and Diabetes; Dept of Paediatric Endocrinology. Barts Health Trust - Royal London Hospital. London, UK; Centre for Endocrinology. William Harvey Research Institute. Barts and The London Medical School. Queen Mary University of London, UK

Hypoparathyroidism is characterized by insufficient secretion of parathyroid hormone (PTH) leading to hypocalcemia, and is diagnosed on biochemical grounds. Low calcium concentrations with concurrent inappropriately low serum PTH concentration are the hallmarks of the disease. There may also be hyperphosphataemia and hypercalciuria.

Hypoparathyroidism in children can have many different etiologies. In adults, hypoparathyroidism is most commonly related to surgery for thyroidectomy, but in children most causes of hypoparathyroidism are related to underlying genetic or immune abnormalities. The hypoparathyroidism can be isolated, as in familial isolated hypoparathyroidism due to GCM2 or PTH gene variants, or autosomal dominant hypocalcaemia (ADH), or part of a syndrome such as DiGeorge Syndrome, CHARGE syndrome, Sanjad-Sankati syndrome, or genetic immune disorders such as APACED syndrome.

ADH1 is caused by Calcium Sensing Receptor (*CaSR*) gain-of-function (GoF) variants, leading to hypoparathyroidism, hypocalcaemia, seizures, hyperphosphatemia, hypomagnesaemia and

severe hypercalciuria, and can lead to isolated hypoparathyroidism. It may have additional features, such as Bartter syndrome.

Many children with hypoparathyroidism present with seizures due to hypocalcaemia.

Conventional treatment of hypoparathyroidism is with Alphacalcidol and Calcium, while ensuring vitamin D concentrations are normal using Cholecalciferol supplementation. This treatment is usually sufficient to stop seizures and normalize hypocalcaemia, but predisposes to hypercalciuria, resulting in nephrocalcinosis and renal impairment. However, this treatment may not be sufficient to stop seizures or symptoms of hypocalcaemia in children with severe hypoparathyroidism.

Treatment with PTH is more physiological, and can improve treatment outcomes. PTH 1-34 has a short half-life, whereas PTH 1-84 has a longer half-life. PTH 1-34 is licenced for the treatment of osteoporosis in adults. Treatment of severe hypoparathyroidism with multiple daily injections of PTH may be effective, but can still lead to inadequate control of symptoms due to its short half-life. PTH 1-84 required less frequent injections, but has been withdrawn from the market.

Continuous subcutaneous infusion of PTH (CSPI) is an option for treatment of severe hypoparathyroidism, and is delivered using insulin pumps. It has been used successfully for severe forms of hypoparathyroidism, but mostly for short periods of time. I will discuss how long-term treatment in a small cohort of patients with ADH1. CSPI by insulin pump effectively increases serum calcium concentrations and reduces seizures, hospital

Correspondencia:

Evelien Gevers

Consultant and Honorary Reader in Paediatric Endocrinology and Diabetes; Barts Health Trust - Royal London Hospital / Centre for Endocrinology, Queen Mary University of London
Mobile: 07906985674

E-mail: evelien.gevers@nhs.net

Secretary endocrinology: Farshana Hussain 02073777000 ext 40418, farshana.hussain@nhs.net

Secretary diabetes: Maggie Murphy, 02073777000, ext 46950, margareth.murphy11@nhs.net

admissions and calcium excretion (mean CSPI duration=3.2±0.6 years), and I will present longer-term data on the safety and efficacy of CSPI in this cohort.

Other treatments, in the form of long acting PTH or inhibition of CaSR activity in ADH1, are potential effective alternatives for refractory or severe hypoparathyroidism. I will discuss new long-acting forms of PTH, their mode of action and the results of recent trials. I will also discuss Encaleret, which inhibits CaSR activity, its mode of action and efficacy in ADH.

References

1. Sun M, Wu X, Yu Y, Wang L, Xie D, Zhang Z, Chen L, Lu A, Zhang G, Li F. Disorders of Calcium and Phosphorus Metabolism and the Proteomics/Metabolomics-Based Research. *Front Cell Dev Biol.* 2020 Sep 10;8:576110. doi: 10.3389/fcell.2020.576110. PMID: 33015068; PMCID: PMC7511772.
2. Khan AA, Bilezikian JP, Brandi ML, Clarke BL, Gittoes NJ, Pasieka JL, Rejnmark L, Shoback DM, Potts JT, Guyatt GH, Mannstadt M. Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop. *J Bone Miner Res.* 2022 Dec;37(12):2568-2585. doi: 10.1002/jbmr.4691. Epub 2022 Nov 14. PMID: 36054621.
3. Hannan FM, Babinsky VN, Thakker RV. Disorders of the calcium-sensing receptor and partner proteins: insights into the molecular basis of calcium homeostasis. *J Mol Endocrinol.* 2016 Oct;57(3):R127-42. doi: 10.1530/JME-16-0124. PMID: 27647839; PMCID: PMC5064759.
4. Theman TA, Collins MT, Dempster DW, Zhou H, Reynolds JC, Brahim JS, Roschger P, Klaushofer K, Winer KK. PTH(1-34) replacement therapy in a child with hypoparathyroidism caused by a sporadic calcium receptor mutation. *J Bone Miner Res.* 2009 May;24(5):964-73. doi: 10.1359/jbmr.081233. PMID: 19063686; PMCID: PMC2672210.
5. Gosmanova EO, Chen K, Rejnmark L, Mu F, Swallow E, Briggs A, Ayodele O, Sherry N, Ketteler M. Risk of Chronic Kidney Disease and Estimated Glomerular Filtration Rate Decline in Patients with Chronic Hypoparathyroidism: A Retrospective Cohort Study. *Adv Ther.* 2021 Apr;38(4):1876-1888. doi: 10.1007/s12325-021-01658-1. Epub 2021 Mar 9. PMID: 33687651; PMCID: PMC8004481.
6. Ketteler M, Chen K, Gosmanova EO, Signorovitch J, Mu F, Young JA, Sherry N, Rejnmark L. Risk of Nephrolithiasis and Nephrocalcinosis in Patients with Chronic Hypoparathyroidism: A Retrospective Cohort Study. *Adv Ther.* 2021 Apr;38(4):1946-1957. doi: 10.1007/s12325-021-01649-2. Epub 2021 Mar 11. PMID: 33704680; PMCID: PMC8004511.
7. Winer KK, Sinaii N, Peterson D, Sainz B Jr, Cutler GB Jr. Effects of once versus twice-daily parathyroid hormone 1-34 therapy in children with hypoparathyroidism. *J Clin Endocrinol Metab.* 2008 Sep;93(9):3389-95. doi: 10.1210/jc.2007-2552. Epub 2008 May 20. PMID: 18492754; PMCID: PMC2567852.
8. Winer KK, Sinaii N, Reynolds J, Peterson D, Dowdy K, Cutler GB Jr. 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.* 2010 Jun;95(6):2680-8. doi: 10.1210/jc.2009-2464. Epub 2010 Apr 14. PMID: 20392870; PMCID: PMC2902068.
9. Winer KK, Kelly A, Johns A, Zhang B, Dowdy K, Kim L, Reynolds JC, Albert PS, Cutler GB Jr. Long-Term Parathyroid Hormone 1-34 Replacement Therapy in Children with Hypoparathyroidism. *J Pediatr.* 2018 Dec;203:391-399.e1. doi: 10.1016/j.jpeds.2018.08.010. PMID: 30470382; PMCID: PMC6298875.
10. Linglart A, Rothenbuhler A, Gueorgieva I, Lucchini P, Silve C, Bougnères P. Long-term results of continuous subcutaneous recombinant PTH (1-34) infusion in children with refractory hypoparathyroidism. *J Clin Endocrinol Metab.* 2011 Nov;96(11):3308-12. doi: 10.1210/jc.2011-1359. Epub 2011 Aug 24. PMID: 21865375.
11. Winer KK, Fulton KA, Albert PS, Cutler GB Jr. Effects of pump versus twice-daily injection delivery of synthetic parathyroid hormone 1-34 in children with severe congenital hypoparathyroidism. *J Pediatr.* 2014 Sep;165(3):556-63.e1. doi: 10.1016/j.jpeds.2014.04.060. Epub 2014 Jun 16. PMID: 24948345; PMCID: PMC4174419.
12. Saraff V, Rothenbuhler A, Högl W, Linglart A. Continuous Subcutaneous Recombinant Parathyroid Hormone (1-34) Infusion in the Management of Childhood Hypoparathyroidism Associated with Malabsorption. *Horm Res Paediatr.* 2018;89(4):271-277. doi: 10.1159/000479867. Epub 2017 Sep 19. PMID: 28926829.

13. Sastre A, Valentino K, Hannan FM, Lines KE, Gluck AK, Stevenson M, Ryalls M, Gorrigan RJ, Pullen D, Buck J, Sankaranarayanan S, Allgrove J, Thakker RV, Gevers EF. PTH Infusion for Seizures in Autosomal Dominant Hypocalcemia Type 1. *N Engl J Med*. 2021 Jul 8;385(2):189-191. doi: 10.1056/NEJMc2034981. PMID: 34233101; PMCID: PMC7614858.
14. Khan AA, Rejnmark L, Rubin M, Schwarz P, Vokes T, Clarke B, Ahmed I, Hofbauer L, Marcocci C, Pagotto U, Palermo A, Eriksen E, Brod M, Markova D, Smith A, Pihl S, Mourya S, Karpf DB, Shu AD. PaTH Forward: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial of TransCon PTH in Adult Hypoparathyroidism. *J Clin Endocrinol Metab*. 2022 Jan 1;107(1):e372-e385. doi: 10.1210/clinem/dgab577. PMID: 34347093; PMCID: PMC8684498.
15. Roberts MS, Gafni RI, Brillante B, Guthrie LC, Streit J, Gash D, Gelb J, Krusinska E, Brennan SC, Schepelmann M, Riccardi D, Bin Khayat ME, Ward DT, Nemeth EF, Roskamp R, Collins MT. Treatment of Autosomal Dominant Hypocalcemia Type 1 With the Calcilytic NPSP795 (SHP635). *J Bone Miner Res*. 2019 Sep;34(9):1609-1618. doi: 10.1002/jbmr.3747. Epub 2019 Jul 26. PMID: 31063613; PMCID: PMC6744344.
16. Khan AA, Rubin MR, Schwarz P, Vokes T, Shoback DM, Gagnon C, Palermo A, Marcocci C, Clarke BL, Abbott LG, Hofbauer LC, Kohlmeier L, Pihl S, An X, Eng WF, Smith AR, Ukena J, Sibley CT, Shu AD, Rejnmark L. Efficacy and Safety of Parathyroid Hormone Replacement With TransCon PTH in Hypoparathyroidism: 26-Week Results From the Phase 3 PaTHway Trial. *J Bone Miner Res*. 2023 Jan;38(1):14-25. doi: 10.1002/jbmr.4726. Epub 2022 Nov 12. PMID: 36271471; PMCID: PMC10099823.
17. Clarke BL, Khan AA, Rubin MR, Schwarz P, Vokes T, Shoback DM, Gagnon C, Palermo A, Abbott LG, Hofbauer LC, Kohlmeier L, Cetani F, Pihl S, An X, Smith AR, Lai B, Ukena J, Sibley CT, Shu AD, Rejnmark L. Efficacy and Safety of TransCon PTH in Adults With Hypoparathyroidism: 52-Week Results From the Phase 3 PaTHway Trial. *J Clin Endocrinol Metab*. 2025 Mar 17;110(4):951-960. doi: 10.1210/clinem/dgae693. PMID: 39376010.
18. Rejnmark L, Gosmanova EO, Khan AA, Makita N, Imanishi Y, Takeuchi Y, Sprague S, Shoback DM, Kohlmeier L, Rubin MR, Palermo A, Schwarz P, Gagnon C, Tsourdi E, Zhao C, Makara MA, Ominsky MS, Lai B, Ukena J, Sibley CT, Shu AD. Palopegteriparatide Treatment Improves Renal Function in Adults with Chronic Hypoparathyroidism: 1-Year Results from the Phase 3 PaTHway Trial. *Adv Ther*. 2024 Jun;41(6):2500-2518. doi: 10.1007/s12325-024-02843-8. Epub 2024 Apr 30. PMID: 38691316; PMCID: PMC11133178.
19. Takacs I, Mezosi E, Soto A, Kamenický P, Figueres L, Galvez Moreno MA, Lemoine S, Borson-Chazot F, Capel I, Ouldrouis T, Lucas N, Allas S, Sumeray M, Ovize M, Mannstadt M. An Open-label Phase 2 Study of Eneboparatide, a Novel PTH Receptor 1 Agonist, in Hypoparathyroidism. *J Clin Endocrinol Metab*. 2024 Aug 13;109(9):2199-2209. doi: 10.1210/clinem/dgae121. PMID: 38449442.
20. Gafni RI, Hartley IR, Roszko KL, Nemeth EF, Pozo KA, Lombardi E, Sridhar AV, Roberts MS, Fox JC, Collins MT. Efficacy and Safety of Encaleret in Autosomal Dominant Hypocalcemia Type 1. *N Engl J Med*. 2023 Sep 28;389(13):1245-1247. doi: 10.1056/NEJMc2302708. PMID: 37754292; PMCID: PMC10616810.