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Pseudohypoparathyroidism In Young Children: Clinical Presentation, Family History, and Challenges to Management

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Introduction

As genetic testing for pseudohypoparathyroidism (PHP) is more widely available, more patients are being diagnosed in younger ages before developing hypocalcemia and hypocalcemia related symptoms. We present 2 cases of young children with different presentations and management challenges.

Case Presentations

Case 1: 23 month (mo) old male, born at 31 weeks, with global developmental delay, obstructive sleep apnea, congenital hypothyroidism (on treatment since 2 mo of age), left inguinal hernia, micropenis (s/p testosterone 50 mg x 3 mo at 18 mo of age), growth hormone (GH) deficiency (started GH since 19 mo of age), and increased weight gain. Noted at 4 months of age to have increased weight for length >99%tile, with BMI >97%tile, z-score >2.

Family history: Mom with history of cyclical Cushing's disease, s/p partial resection pituitary and adrenals, hypothyroidism, osteoma cutis, granuloma annulare, and brachydactyly.

GNAS gene sequencing showed a pathogenic variant consistent with PHP type 1a. Skeletal survey with brachycephaly, otherwise normal. PTH levels elevated, calcium, phosphorus, and 25-hydroxy vitamin D were normal. Patient started on calcium and calcitriol treatments.

Case 2: 12 mo old male with family history of PHP presenting to clinic with abnormal genetic testing, showing *STX16* pathogenic variant, consistent with PHP type 1b. Born at 38 weeks, mom on calcium citrate, calcitriol and levothyroxine during pregnancy. Normal birth weight and length, no developmental delay, no seizures. During his initial evaluation, his weight for length was noted over 99%tile, BMI >99%tile, z-score >3, with increased weight gain since 6 months of age.

Family history: Mom herself was diagnosed with PHP at 6y of age, presenting initially with seizures. Family history includes positive genetic testing in patient's maternal uncle and maternal cousin. Also, patient's maternal grandmother and great aunts are carriers of the inherited mutation from maternal grandfather.

Initial labs were normal, however subsequent labs at 20 months old showed elevated PTH, and thus started on calcium, and eventually calcitriol.

Results

Fig 1a-c: Case 1 (PHP type 1a) growth charts

Fig. 1a Length 0-2 year of age, WHO curve

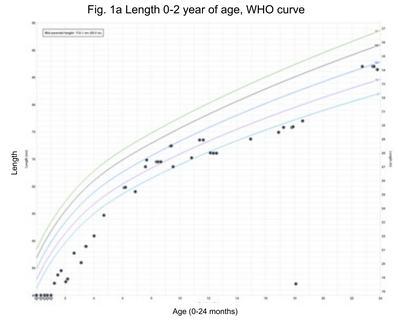

Fig. 1b Weight 0-2 year of age, WHO curve

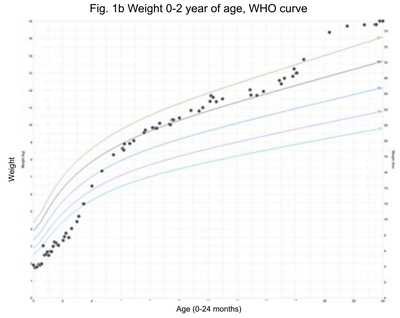

Fig. 1c Weight-for-Length, 0-2 year of age, WHO curve

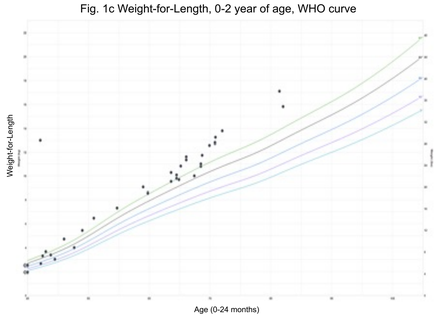

Table 1a-d: Case 1 labs

Table 1a: PTH, calcium levels prior and on treatment

	5/2023 (18mo of age) Started calcium carbonate (CaCO3) 36 mg/kg/d and calcitriol 0.25 mcg BID (0.036 mcg/kg/d)	**9/2023** Decreased calcitriol to 0.25 mcg daily (0.016 mcg/kg/d)	**12/2023** Increase CaCO3 (40 mg/kg/d)
PTH (pg/mL)	**317 (H)** *(12-55)*	**129.9 (H)** *(16-63)*	**267 (H)** *(16-63)*
Calcium (mg/dL)	9.4 *(8.5-10.6)*	9.7 *(8.7-9.8)*	9.0 *(8.7-9.8)*
Phosphorus (mg/dL)	6.8 *(3.5-6.8)*	7.9 (H) *(3.5-6.8)*	8.1 (H) *(3.5-6.8)*
Albumin (g/dL)	4.5 *(3.5-4.7)*	4.5 *(3.6-5.1)*	3.4 *(3.5-4.7)*
Vit D (ng/mL)	42		**27 (L)**

Table 1b: Initial thyroid hormone levels before treatment

	11/2021	**12/2021**	**1/2022 (2 mo of age, corrected 40 week gestation)** Started levothyroxine
TSH (0.7-4.8 uIU/mL)	**10.89 (H)**	**7.095 (H)**	**10.45 (H)**
Free T4 (0.8-2.0 ng/dL)	1.0	1.0	**0.7 (L)**

Table 1c: GH and 1mcg ACTH stimulation tests before treatment

	5/2023 (18mo)
GH stim test (glucagon, clonidine) (human growth hormone ng/mL)	Peak **3.8**
1mcg ACTH stim test (cortisol ug/dL)	6.8→21.6→24.7

Table 1d: Initial puberty hormones before treatment

	5/2023 (18mo)
LH (mIU/mL)	<0.2
FSH (mIU/mL)	<0.7
Testosterone (ng/dL)	<4.3

Results cont'd

Fig 2a-c: Case 2 (PHP type 1b) growth charts

Fig. 2a Length 0-2 year of age, WHO curve

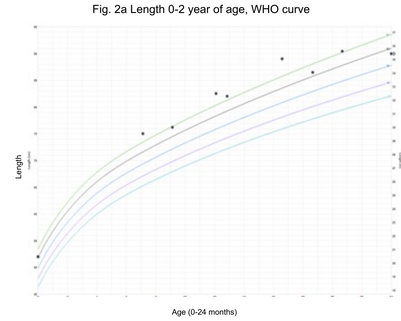

Fig. 2b Length 0-2 year of age, WHO curve

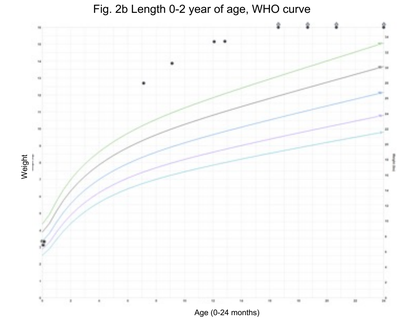

Fig. 2c Weight-for-Length 0-2 year of age, WHO curve

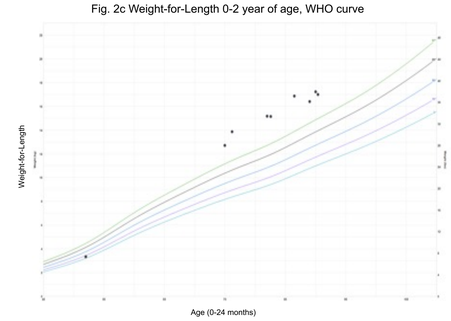

Table 2a-b: Case 2 labs

Table 2a: PTH, calcium levels prior and on treatment

	11/2020	**10/2021 (2yr of age)** Started CaCO3 (26 mg/kg/d)	**4/2022** Increase CaCO3 (32 mg/kg/d)	**6/2022** Added calcitriol 0.25 mcg daily (0.013 mcg/kg/d)	**8/2022**	**1/2023**	**8/2023**	**12/2023** Increase CaCO3 (40 mg/kg/d)
PTH (pg/mL)	32 *(12-55)*	**74 (H)** *(12-55)*	**84 (H)** *(14-66)*	**95 (H)** *(14-66)*	**74 (H)** *(14-66)*	41 *(14-66)*	**73 (H)** *(14-66)*	**93 (H)** *(14-66)*
Calcium (mg/dL)	9.8 *(8.5-10.6)*	9.8 *(8.5-10.6)*	9.7 *(8.5-10.6)*	9.8 *(8.5-10.6)*	9.5 *(8.5-10.6)*	9.6 *(8.5-10.6)*	9.6 *(8.5-10.6)*	9.8 *(8.9-10.4)*
Phosphorus (mg/dL)	6.2 *(4-8)*	5.6 *(4-8)*	6.1 *(4-8)*	5.1 *(4-8)*	6.0 *(4-8)*	5.6 *(3-6)*	5.1 *(3-6)*	5.0 *(3-6)*
Albumin (g/dL)	4.4 *(3.6-5.1)*	4.7 *(3.6-5.1)*	4.7 *(3.6-5.1)*	4.6 *(3.6-5.1)*	4.5 *(3.6-5.1)*	4.6 *(3.6-5.1)*	4.6 *(3.6-5.1)*	4.7 *(3.6-5.1)*
Vit D (ng/mL)	60	31						

Table 2b: Thyroid hormone level monitoring, not on treatment

	11/20/23	**4/2021**	**10/2021**	**4/2022**	**1/2023**	**8/2023**	**1/2024**
TSH (0.5-4.3 uIU/mL)	4.22	4.13	5.03 (H)	5.4 (H)	5.9 (H)	6.78 (H)	3.48
FreeT4 (0.9-1.4 ng/dL)	1.0	1.1	1.0	1.0	1.1	1.0	1.2

Discussion

Both cases had early onset obesity even before 1 year of age, and significant family history suggestive of PHP. Case 1 in addition had multiple hormone abnormalities consistent with diagnosis. It is important to diagnose PHP early to start treatment, to avoid chronically elevated PTH, and possibly prevent severe hypocalcemia and hyperphosphatemia. Long standing PTH excess may have adverse effects on skeletal mineralization and growth. Thus, it is recommended to start calcium and/or calcitriol once PTH is increased, even prior to hypocalcemia development.

Also, early onset obesity is important to manage with lifestyle interventions, with early dietitian involvement. However medical management of obesity is limited in this age which makes management challenging.

Conclusion

Pseudohypoparathyroidism should be considered in a young child with early onset obesity and suggestive family history, also if patient has various hormone abnormalities.

References

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