A rare combination of autoimmune, cardiac, and reproductive anomalies in a child with pseudohypoparathyroidism type 1a/1c

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ABSTRACT

Background: Recurrent Hypocalcemic Tetany in children is an important clinical feature of pseudohypoparathyroidism encompassing a spectrum of rare endocrine disorders characterised by end-organ resistance to parathyroid hormone (PTH).

Case presentation: We report a case of a 10-year-old girl with genetically confirmed PHP Type 1a and 1c, presenting with classical features including recurrent hypocalcemic tetany, short stature, and mild intellectual delay. Notably, the child exhibited additional findings of primary hypothyroidism, celiac disease, positive autoimmune markers (ANA, SSA/Ro, Ro-52), congenital heart disease (ventricular septal defect), and Müllerian duct anomalies - features rarely reported in conjunction with pseudohypoparathyroidism.

Conclusion: The co-existence of autoimmune endocrinopathy, congenital cardiac defect, and Müllerian anomaly in our patient raises the possibility of an expanded phenotypic spectrum or dual genetic pathology. The constellation of findings in this child may suggest either an represent coincidental conditions or a blended/dual genetic diagnosis.

Keywords: Pseudohypoparathyroidism, Mayer–Rokitansky–Küster–Hauser, Autoimmune, case report

Type of Article: CASE REPORT **Specialty:** Endocrinology

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Background

Pseudohypoparathyroidism (PHP) is a heterogeneous group of disorders caused by impaired signaling in the GNAS-cAMP pathway, leading to resistance to PTH and other hormones such as TSH [1]. PHP Type 1a and 1c share clinical features, including hypocalcemia, hyperphosphatemia, and Albright hereditary osteodystrophy (AHO) traits, although they are biochemically distinguished by Gsα protein activity [2]. While endocrine and skeletal features of PHP are well described, coexistence with cardiac anomalies, autoimmune diseases, and genital tract malformations are exceedingly rare and raises questions about overlapping genetic or developmental syndromes [3]. Here, the authors present a case of a 10-year-old female with multi system involvement of the affected gene.

Case Summary, Investigations and Management

A 10-year-old female child was brought to the paediatric emergency with complaints of fever and excessive irritability for 5 days, dizziness, and multiple episodes of projectile vomiting since one day. She has had multiple episodes of painful body spasms of both hands for the past four years, which were misdiagnosed as seizure episodes. There was no history of trauma, tinnitus, focal neurologist deficit, pain behind eyes, consumption of any poisonous substance in the past. She was born out of non consanguineous marriage via emergency caesarean section in view of fetal bradycardia, second birth order, and was fully immunised for age. There was no history of any chronic illness in the family. She studies in 5th standard and was developmentally normal. On examination, child's general condition was fair with pallor, and no icterus, clubbing, cyanosis, lymphadenopathy, or edema. She had a round, chubby face, had bilateral parotid enlargement (Figure1), and had short stature. Vitals were stable. On CNS examination, GCS 15/15, conscious, well oriented to time, place, and person, no involvement of cranial nerves, sensory and motor system examination was within normal limits. There was no cerebellar involvement. CVS examination revealed a pansystolic murmur in the mitral area, no heave or thrust. The respiratory system, abdominal examination, were unremarkable. On sexual maturity rating by tanner staging she was tanner stage 2. The Trousseau sign and Chvostek sign were positive implying clinical evidence of

hypocalcemia. Laboratory evaluations are summarised in Table 1, revealing anaemia, hypocalcemia with elevated PTH, low vitamin D levels, and biochemical evidence of hypothyroidism. The autoimmune work-up was positive for anti-nuclear antibodies, anti-SSA/Ro, anti-SSB/La, and Ro-52 antibodies. Ophthalmological evaluation showed no evidence of decreased tear production, and dental evaluation suggested no evidence of caries. IgA tissue transglutaminase suggested gluten hypersensitivity. Magnetic resonance imaging (MRI) (Figure 2a and b) of the brain revealed bilateral globus pallidus hyperintensities, implying mineral deposition. Echocardiography identified a sub-aortic restrictive ventricular septal defect with mild aortic regurgitation, which was not hemodynamically significant and not requiring surgical intervention. Ultrasonography and MRI of the pelvis revealed a hypoplastic uterus consistent with Müllerian agenesis (MRKH-like phenotype), likely type 1 MRKH. Gene analysis confirmed a GNAS loss-of-function mutation, establishing the diagnosis of pseudohypoparathyroism

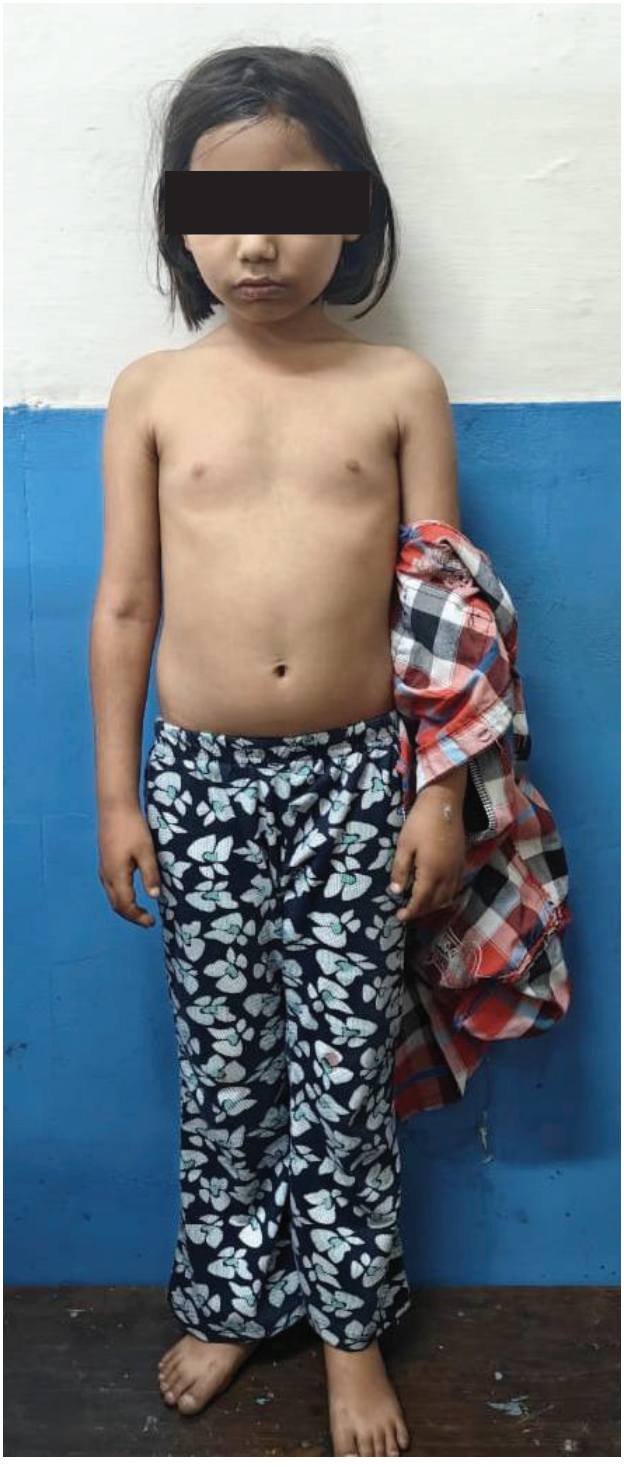

Figure 1. *Short, chubby appearance of the child.*

Table 1. *Biochemical investigations.*

Lab parameter	Value	Normal range
Hb(mg/dL)	**8.2**	12.5-16.1
TLC(CELLS/CUMM)	3400	4000-10500
DLC(NEUTROPHILS/ LYMPHOCYTES/ MONOCYTES/ BASOPHILS)	16/74/5/1	
PLATELETS($10^{3/}$ MICROLITRE)	1.4	1.5-4
AST/ALT(U/l)	150/104	5-45/10-40
BLOOD UREA/ SERUM CREATININE(mg/dl/ mg/dl)	4/0.3	7-18 0.31-0.88
TOTAL PROTEIN(g/l)	8.3	6.4-8.1
SERUM ALBUMIN(g/l)	3.5	3.5-5.6
Ca2+/PHOSPHATE/ ALP(mg/dl//mg/dl//IU/L)	**5.2/3.4/0.9**	8.8-10.8/3.7-5.6/140-560
IgA-tTg	**+**	Negative
DCT	negative	Negative
VITAMIN D(ng/ml)	**8**	30-50
VITAMIN B 12(pg/ml)	720	190-250
FOLATE(ng/ml)	9.5	3-17
iPTH(pg/ml)	**395.9**	10-65
IgM FOR LEPTOSPIROSIS/ BRUCELLA/SCRUB TYPHUS	Negative	Negative
ANTI NUCLEAR ANTIBODY	**+**	
SSA/SSB	**+/+**	
Ro 52	**+**	
Luteinising hormone(IU/l)	1.29	0.03-3.7
Follicle stimulating hormone(mU/ml)	3.21	0.3-10
Serum estradiol(pg/ml)	29.8	24-60
Serum testosterone(ng/ dl)	6.0	<30
HbA1c(%)	5.65	<5.7
Serum TSH	**17**	**0.4-5**
Serum fT4(mcg/dl)	2.08	4.5-12
Serum fT3(Ng/dl)	5.02	2.3-4.2
Ferritin(ng/ml)	4.25	10-200

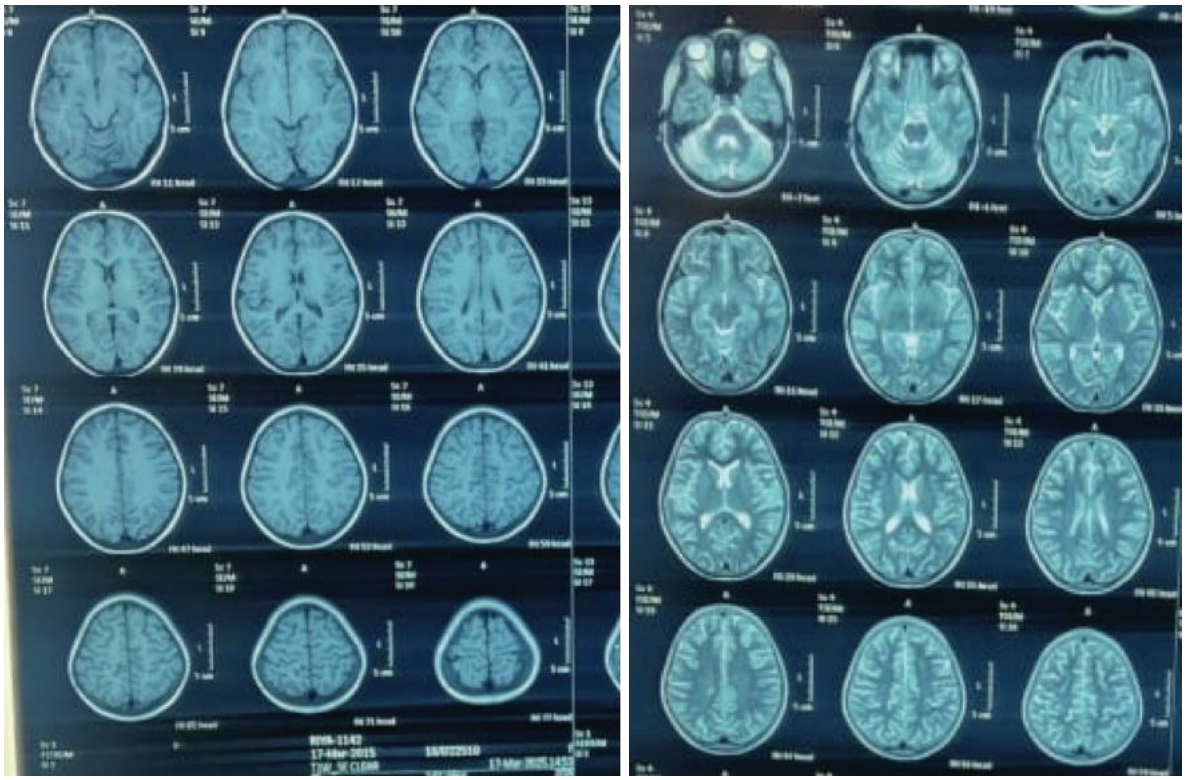

Figure 2. *(a) T1 weighted MRI brain showing increased signal in bilateral basal ganglia. (b) T2 weighted MRI brain showing decreased signal intensity in bilateral basal ganglia.*

Type 1a/1c. The patient was managed with intravenous calcium, vitamin D supplementation (calcitriol at 0.5mcg/day, single dose), levothyroxine (50mcg/day, single dose), anti-epileptic medications (levetiracetam @ 20mg/kg/day in two divided doses), and hydroxychloroquine (5mg/kg/day, single dose). She showed significant improvement in the spasms with eventual normocalcemia and was later switched to oral calcium, anti epileptics were stopped in view of discovery of the cause of spasms. She was discharged on oral calcium, calcitriol, levothyroxine, hydroxychloroquine, and advised gluten-free diet and regular cardiology follow up and doing well on 12 month follow up. She has gained 2cm over 12 months; however had not attained menarche at last follow up.

Discussion

Symptomatic hypocalcemia is frequently encountered in the Emergency Department, necessitating admission having varied etiologies, with hypoparathyroidism and vitamin D deficiency being the most common causes [4]. However, rarer etiologies such as PHP, as was present in our index case, should be worked up for. The word PHP was first described by Albright et al in 1942. PHP type 1A (PHP 1A) is a rare endocrine disorder resulting from a loss-of-function mutation in the GNAS1 gene, which encodes the α-subunit of the stimulatory G-protein (Gsα) [5]. This defect impairs cAMP-mediated signaling in hormone- responsive tissues, leading to resistance to multiple hormones including parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), and growth hormone-releasing hormone (GHRH) [6]. The hallmark clinical features include hypocalcemia, hyperphosphatemia, hypothyroidism, and short stature, often accompanied by the characteristic Albright hereditary osteodystrophy (AHO) phenotype, including round facies, brachydactyly, and cognitive impairment [7]. Cases with GNAS mutations have diverse clinical phenotypes, and hormone resistance can be detected at different stages of life with large individual differences. The onset of PTH resistance is usually delayed and may not be discovered until childhood, adolescence, or even adulthood. This latency of PTH resistance may be due to a gradual development of paternal Gsα silencing in the maternally imprinted tissues [3]. Besides PTH, resistance to other hormones may also be seen. Among them, TSH resistance is the most common and usually the first to be discovered. A case of PHP type 1a in a 21-year-old confirmed by clinical, biochemical, and molecular analyses has been reported. Patients with PHP have various endocrinopathies from early childhood to adulthood, which yield a highly heterogeneous clinical picture [8]. Early interventions and multidisciplinary follow-up are necessary for efficient therapeutic management of PHP type 1a. There is a reported case of a 12-year-old who presented with difficulty walking, spasms of all 4 limbs, who had the classical signs of hypocalcemia and raised PTH, with neuroimaging suggesting basal ganglia calcifications, hence confirming the diagnosis of PHP. In this case, the

child presented with classic biochemical findings of PHP alongside multiple autoimmune manifestations, which are increasingly recognized in patients with GNAS mutations. The positive antiSSA, anti-SSB, Ro-52 antibodies, and ANA may point toward an autoimmune overlap syndrome, potentially Sjögren's syndrome, though uncommon in this age group [9]. The existence of a cardiac anomaly may represent a coincidental association or might represent a developmental association with GNAS mutation.

Literature [10,11] suggests that Gsα signaling plays a role in immune regulation, and disruption may predispose to autoimmunity through altered T- and B-cell function. A few reports have suggested associations of GNAS mutations with autoimmune polyendocrinopathy. The discovery of a hypoplastic uterus in pelvic imaging may suggest an underlying and unproven endocrine overlap. While Müllerian agenesis or hypoplasia, as seen in Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome, are not directly linked to GNAS mutations, hypogonadotropic hypogonadism and delayed or abnormal pubertal development have been observed in PHP due to resistance to gonadotropins. In this case, the primary uterine anomaly may be hypothesised to occur due to hormonal resistance, rather than a true congenital agenesis, although a coincidental Müllerian anomaly cannot be ruled out.

The occurrence of *GNAS*-related PHP with multisystem involvement in a single paediatric patient is exceedingly rare. The co-existence of autoimmune endocrinopathy, congenital cardiac defect, and Müllerian anomaly in our patient raises the possibility of an expanded phenotypic spectrum or dual genetic pathology [11]. The constellation of findings in this child - especially the presence of autoimmunity, congenital cardiac defect, and Müllerian anomalies - is unusual for isolated PHP, and these findings may suggest either an represent coincidental conditions or a blended/dual genetic diagnosis. This case reinforces the necessity for a multidisciplinary diagnostic approach when encountering hypocalcemia with atypical systemic features. The discovery of a primary structural uterine anomaly in pelvic imaging may further support an endocrine overlap [12]. Cardiac and genital anomalies are not classical features of PHP, although GNAS expression in various embryological tissues may play a role in broader developmental pathways. The autoimmune findings (celiac disease, ANA/SSA/Ro-52) raise the possibility of Autoimmune Polyglandular Syndrome (APS) overlap or a generalized immune dysregulation [13]. Only a few such cases with similar multisystem involvement have been reported in the literature, and none with this complete constellation, underscoring the rarity of this case [14]. The short-term follow-up, single case nature, further lack of developmental studies delineate the limitations of this case. Furthermore, the analysis of the whole genome was considered and may have provided more evidence to the coexistence of these findings in the above case, however due to financial constraints it could not be performed.

Conclusion

GNAS mutations may present beyond classic features of PHP, involving autoimmune endocrinopathies. Autoimmunity may occur in the setting of GNAS loss-of-function, suggesting an expanded immunological role of Gsα signaling pathway. Cardiac and reproductive anomalies, although rare, may co-exist and hence should be proactively evaluated.

What is new?

This report emphasises the importance of multidisciplinary evaluation in children with pseudohypoparathyroidism presenting with atypical systemic features, as it may uncover previously unrecognised associations or blended genetic pathology. The coexistence of autoimmune markers (ANA, SSA/Ro-52) and celiac disease suggests a potential immune dysregulation related to GNAS pathway abnormalities, which has been rarely described.

List of Abbreviations

AHO	Albright Hereditary Osteodystrophy
Anti SSA / Anti SSB	Anti-Sjögren's Syndrome type A antibody/ Anti-Sjögren's Syndrome type B antibody
cAMP	Cyclic Adenosine Monophosphate
CNS	Central Nervous System
CVS	Cardiovascular System
DCT	Direct coombs test
GCS	Glasgow Coma Scale
GNAS	Guanine Nucleotide-binding protein, Alpha Stimulating activity polypeptide
MRKH	Mayer–Rokitansky–Küster–Hauser
PHP	Pseudohypohypoparathyroidism
PTH	Parathormone
TSH	Thyroid Stimulating Hormone

Informed Consent

We, the authors, certify that we have obtained all appropriate, informed written parental consent prior to publication. The parents have given their written informed consent for images and other clinical information to be reported in the journal. The parents understand that their or their child's names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Ethical Approval

Ethical approval is not required at our institution to publish an anonymous case report.

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TIMELINE

~6 years of age	Onset of recurrent painful spasms of both hands; episodes misdiagnosed as seizures
10 years (5 days prior to admission)	Fever and excessive irritability
10 years (1 day prior to admission)	Dizziness and multiple episodes of projectile vomiting
Day 0 (Emergency admission)	Examination revealed short stature, round facies, bilateral parotid enlargement, positive Chvostek and Trousseau signs, pansystolic murmur
INVESTIGATIONS [DAY 1–14]	Laboratory evaluation showed hypocalcemia, elevated PTH, vitamin D deficiency, hypothyroidism, and anemia Autoimmune work-up positive for ANA, anti-SSA/Ro, anti-SSB/La, and Ro-52 antibodies; IgA tissue transglutaminase suggestive of gluten hypersensitivity MRI brain showed bilateral globus pallidus mineral deposition Echocardiography revealed sub-aortic restrictive VSD with mild aortic regurgitation
DIAGNOSIS	Rare Combination of Autoimmune, Cardiac, and Reproductive Anomalies in a Child with PHP Type 1a/1c
TREATMENT	Initiation of intravenous calcium, calcitriol, levothyroxine, levetiracetam, and hydroxychloroquine
Discharge	Oral calcium, calcitriol, levothyroxine, hydroxychloroquine; advised gluten-free diet and cardiology follow-up
12-month follow-up	Clinically stable, normocalcemia maintained, 2 cm height gain; no attainment of menarche

References

1. Zygmunt A, Pacocha M, Domanska-Czajka A, Skowronska-Jozwiak E, Lupinska A, Stawerska R, et al. Analysis of the prevalence and incidence of pseudohypoparathyroidism in Poland based on National Health Fund data with clinical presentation of own cases. Front Endocrinol (Lausanne). 2025;16:1584154. https://doi.org/10.3389/fendo.2025.1584154
2. Wan J, He D, Xie J, Chen Z. A novel GNAS mutation in pseudohypoparathyroidism type 1a with articular flexion deformity: a case report. Open Life Sci. 2024;19(1):20220918. https://doi.org/10.1515/biol-2022-0918
3. Cipriano L, Ferrigno R, Andolfo I, Russo R, Cioffi D, Savanelli MC, et al. Genotype -Phenotype Correlation of GNAS Gene: review and Disease Management of a Hotspot Mutation. Int J Mol Sci. 2024;25(20):10913. https://doi.org/10.3390/ijms252010913
4. Takatani R, Minagawa M, Nakamura A, Matsumoto K, Takagi M, Hasegawa Y. A case of pseudohypoparathyroidism type 1A initially diagnosed as pseudohypoparathyroidism type 1B: clinical and molecular overlap. Endocr J. 2018;65(7):729–36.
5. Bastepe M, Jüppner H. GNAS locus and pseudohypoparathyroidism. Horm Res. 2005;63(2):65–74. https://doi.org/10.1159/000083895
6. Elli FM, Linglart A, Garin I, de Sanctis L, Bordogna P, Grybek V, et al. The prevalence of GNAS deficiency-related diseases in a large cohort of patients characterised by the EuroPHP Network. J Clin Endocrinol Metab. 2016;101(10):3657–68.
7. Levine MA. Clinical and molecular aspects of pseudohypoparathyroidism. J Endocr Soc. 2019;3(4):1036–48.
8. Wen T, Liu Q, Liu X, You R, Li X, Li R, et al. Atypical presentation of pseudohypoparathyroidism with absence of mutations in the GNAS gene: a case report. BMC Endocrine Disord. 2025;25(1):104. https://doi.org/10.1186/s12902-025-01933-0
9. Chtioui S, Ali ZAS, Alahyane M, Rafi S, Mghari GE, Ansari NE. Pseudohypoparathyroidism and Albright hereditary osteodystrophy: a case report and literature review. Scholars J Med Case Rep. 2023;11(2):150–3. https://doi.org/10.36347/sjmcr.2023.v11i02.014
10. Gálvez GL, Roblero JEG. Pseudohypoparathyroidism type 1A and Albright hereditary osteodystrophy: a comprehensive review of molecular pathogenesis, clinical manifestations, and therapeutic approaches. Int J Res Med Sci. 2025;13(7):3097–102.
11. Linglart A, Levine MA, Jüppner H. Pseudohypoparathyroidism. Endocrinol Metab Clin North Am. 2018;47(4):865–88. https://doi.org/10.1016/j.ecl.2018.07.011
12. Turan S, Bastepe M. GNAS Spectrum of Disorders. Curr Osteoporos Rep. 2015;13(3):146–58. https://doi.org/10.1007/s11914-015-0268-x
13. Mantovani G, De Sanctis L, Barbieri AM, Elli FM, Bollati V, Vaira V, et al. Pseudohypoparathyroidism and GNAS epigenetic defects: clinical evaluation of albright hereditary osteodystrophy and molecular analysis in 40 patients. J Clin Endocrinol Metab. 2010;95(2):651–8. https://doi.org/10.1210/jc.2009-0176
14. Sippelli F, Briuglia S, Ferraloro C, Capra AP, Agolini E, Abbate T, et al. Identification of a novel GNAS mutation in a family with pseudohypoparathyroidism type 1A. BMC Pediatrics. 2024;24(1):271. https://doi.org/10.1186/s12887-024-04761-8

Summary of the case

1	**Patient (gender, age)**	10 year, female
2	**Final Diagnosis**	A Rare Combination of Autoimmune, Cardiac, and Reproductive Anomalies in a Child with Pseudohypoparathyroidism Type 1a/1c
3	**Symptoms**	fever and excessive irritability for 5 days, dizziness and multiple episodes of projectile vomiting
4	**Medications**	intravenous calcium, vitamin D supplementation (calcitriol at 0.5mcg/day, single dose), levothyroxine(50mcg/day, single dose), anti-epileptic medications(levetiracetam @ 20mg/kg/day in two divided doses), and hydroxychloroquine (5mg/kg/day, single dose). She showed significant improvement and is doing well on follow-up, with normocalcemia.
5	**Clinical Procedure**	Relevant biochemical and radiological investigations
6	**Specialty**	Endocrinology, rheumatology