Clinical Case Report

Medicine®

OPEN

A typical 22q11.2 deletion syndrome and pseudohypoparathyroidism

A CARE compliant case report

Xi-Juan Liu, MD[a], Chen Yan, PhD[b], Jing-Yu Jia, PhD[c,*]

Abstract

Rationale: It is rare to find 22q11.2 deletion syndrome with pseudohypoparathyroidism in children. Furthermore, the phenotypic spectrum of this disorder varies widely.

Patient concerns: A patient was diagnosed with pseudohypoparathyroidism at age 14 years because of convulsions, hypocalcemia, hyperphosphatemia, normal parathyroid hormone levels, and basal ganglia calcifications. Thereafter, the child presented with symptoms of nephrotic syndrome; subsequently, he was diagnosed with nephrotic syndrome at the local hospital.

Diagnosis: At our hospital, multiplex ligation-dependent probe amplification confirmed that the patient had 22q11.2 deletion syndrome.

Interventions: The patient continued to be treated with calcium supplements.

Outcomes: Seizure activity and proteinuria ceased.

Lessons: Signs of this syndrome include delayed speech development due to velofacial dysfunction, recurrent croup attacks during early childhood due to latent hypocalcemia, and mild dysmorphic features. The findings of this patient indicated that 22q11.2 deletion syndrome may include a wide spectrum of clinical findings and that this diagnosis needs to be considered for all patients presenting with hypocalcemia, regardless of age.

Abbreviations: MPLA = multiplex ligation-dependent probe amplification, OMIM = Online Mendelian Inheritance in Man, PTH = parathyroid hormone.

Keywords: 22q11.2 deletion syndrome, diagnosis, hypocalcemia, nephrotic syndrome, pseudohypoparathyroidism

1. Introduction

The 22q11.2 deletion syndrome (Online Mendelian Inheritance in Man [OMIM] 611867, also known as velocardiofacial syndrome [OMIM 192430] or DiGeorge syndrome [OMIM 188400]) is caused by a microdeletion (1.5–3 Mb) of chromosome 22 and has an estimated prevalence of 1 in 4500 live births.[1,2] This disorder is rare. The phenotypic spectrum of 22q11.2 deletion syndrome demonstrates wide variability and could present at any age. Phenotypes include congenital cardiovascular anomalies (74% of patients), craniofacial anomalies (the majority of patients), palatal anomalies (69%), immunodeficiency (77%), developmental delay or learning disabilities (70%–90%), and hypocalcemia associated with hypoparathyroidism (50%).[3] Usually, 22q11.2 deletion syndrome can be diagnosed when the patient exhibits congenital cardiovascular anomalies coupled with other phenotypes during childhood. We report a boy who presented with seizures due to hypocalcemia as a result of pseudohypoparathyroidism. He was diagnosed with pseudohypoparathyroidism because of his convulsions, hypocalcemia, hyperphosphatemia, normal parathyroid hormone levels, and basal ganglia calcifications. Hypocalcemia is not caused by nephrotic syndrome. Moreover, long-term hypocalcemia causes renal dysfunction, which appears to be a clinical feature of nephrotic syndrome. Later, the child exhibited symptoms of nephrotic syndrome, which was subsequently diagnosed at a local hospital. However, at our hospital, multiplex ligation-dependent probe amplification (MPLA) confirmed that he had 22q11.2 deletion syndrome.

2. Case report

A 14-year-old boy with proteinuria was referred to our hospital. He was born at term by vaginal delivery, with a birth weight of 3500 g. No cardiovascular abnormalities or cleft palate had been

Editor: N/A.

This study was supported by grant from the National Nature Science Foundation of China (NO. 81360268) and project of Science and Technology Department of Jiangxi Province (NO. 20161BAB215245).

The patient and his parents provided informed consent for publication of his case.

The authors have no conflicts of interest to disclose.

[a] Department of Paediatric, [b] Department of Rheumatology, [c] Department of Orthopaedics, The Second Affiliated Hospital of Nanchang University, Nanchang City, China.

[*] Correspondence: Jing-Yu Jia, Department of Orthopaedics, The Second Affiliated Hospital of Nanchang University, Nanchang City, 330006, China (e-mail: liuxijuan9@163.com).

Medicine (2019) 98:25(e16109)

Received: 24 December 2018 / Received in final form: 22 April 2019 / Accepted: 17 May 2019

http://dx.doi.org/10.1097/MD.0000000000016109

Table 1

Serum biochemistry of the patient at presentation.

Project name	Results	Nomal ranges
Total calcium, mmol/L	1.87	2.23–2.8
Ionized calcium, mmol/L	0.83	1.12–1.23
Phosphorus, mmol/L	1.94	0.9–1.34
Alkaline phosphatase, U/L	89	<150
Magnesium, mmol/L	0.74	0.6–1.1
Albumin, g/L	31.35	38–54
PTH, pg/mL	27.28	15–65
25 OH D3, ng/mL	11.84	>20
Total cholesterol, mmol/L	5.27	<5.2
Urine protein, mg/24h	3000.5	<150
Proteinuria, g/L	++++	–
Growth hormone, ng/mL	19.45	0.55–4.74
FT3, pg/mL	3.71	2.3–4.2
FT4, ng/dL	1.1	0.89–1.8
TSH, mIU/L	4.325	0.55–4.78

Figure 2. The deformity of shortened fourth and fifth metacarpals and metatarsal was not observed through wrist X-ray.

detected during any routine medical examinations. He had no history of feeding problems, such as regurgitation, and there were no symptoms of hypocalcemia during early infancy. Furthermore, he had no history of neck surgery. His neuromotor development was slightly delayed, with particular delays in the emergence of language. The patient walked at age 2 years and spoke his first words at age 2.6 years. Upon presentation at our hospital, his height was 150 cm, and his weight was 65 kg. His learning ability was slow, and he finished regular middle school with the lowest achievement scores. He also had the following typical features of craniofacial anomalies: round face, short neck, protrusion of the forehead, bulbous nasal tip, and flat nasal root. His fingers and toes did not have any deformities. No abnormality was found during neurological examination. His parents and 5 siblings were alive and well, and no other family members or relatives were clinically affected.

The patient was referred to the local hospital because of eyelid edema. Laboratory studies demonstrated massive proteinuria (3006.9 mg/24 h [<150]), hypoproteinemia (28.4 g/L [38–54]), and hyperlipidemia (6.71 mmol/L [<5.2]). Therefore, he was diagnosed with nephrotic syndrome at the local hospital. He was administered hormone therapy for 2 months, but his urine still had proteinuria; therefore, he was referred to our hospital. His parents stopped his hormone therapy for 2 weeks because of the side effects. He had proteinuria when he presented to our hospital. During hospitalization, focal seizure activity with brief jerking of his left arm and leg developed.

At our hospital, an electroencephalogram confirmed the presence of seizures, and laboratory study results demonstrated hypocalcemia, hyperphosphatemia, normal parathyroid hormone (PTH) levels, and alkaline phosphatase (Table 1). Magnetic resonance imaging demonstrated focal ischemia of the cerebral cortex, a mucous cyst in the right maxillary sinus, and bilateral otitis media (Fig. 1A and B). Computed tomography showed right basal ganglia calcifications (Fig. 1C). Chvostek and Trousseau signs were positive. No deformity of the shortened fourth and fifth metacarpals and metatarsal was observed during radiography of the wrist (Fig. 2). Pseudohypoparathyroidism was diagnosed and treated with calcium and active vitamin D supplements. The patient had no eyelid edema at our hospital. Doppler ultrasound did not show any congenital deformity of the urinary system. Laboratory study results did not demonstrate proteinuria, hypoproteinemia, or hyperlipidemia at our hospital. Therefore, we did not diagnose nephrotic syndrome. Because the child presented with lesions on multiple organs, multiplex ligation-dependent probe amplification was performed. Finally,

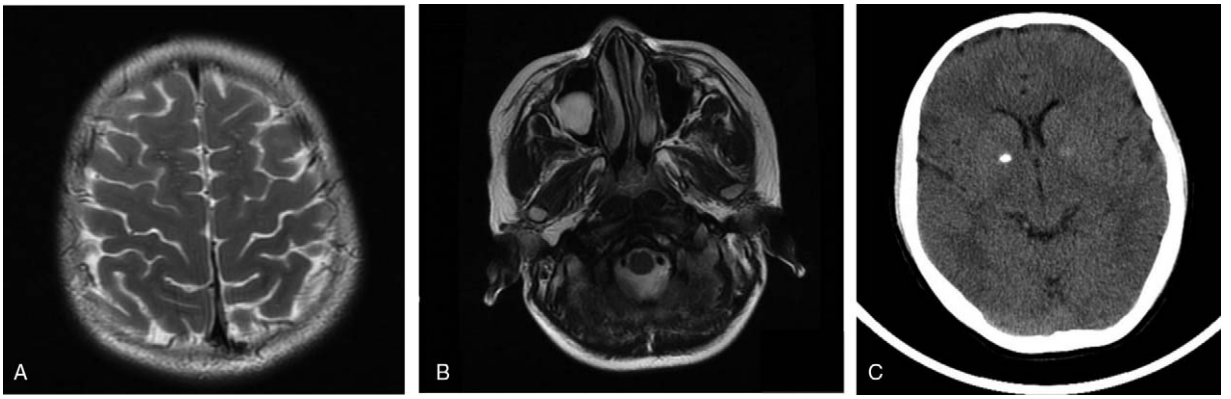

Figure 1. A. MRI T2 demonstrated focal ischemia of cerebral cortex. B. MRI T1 presented right maxillary sinus mucocele and bilateral otitis me dia. C. CT shows the basal ganglia calcification.

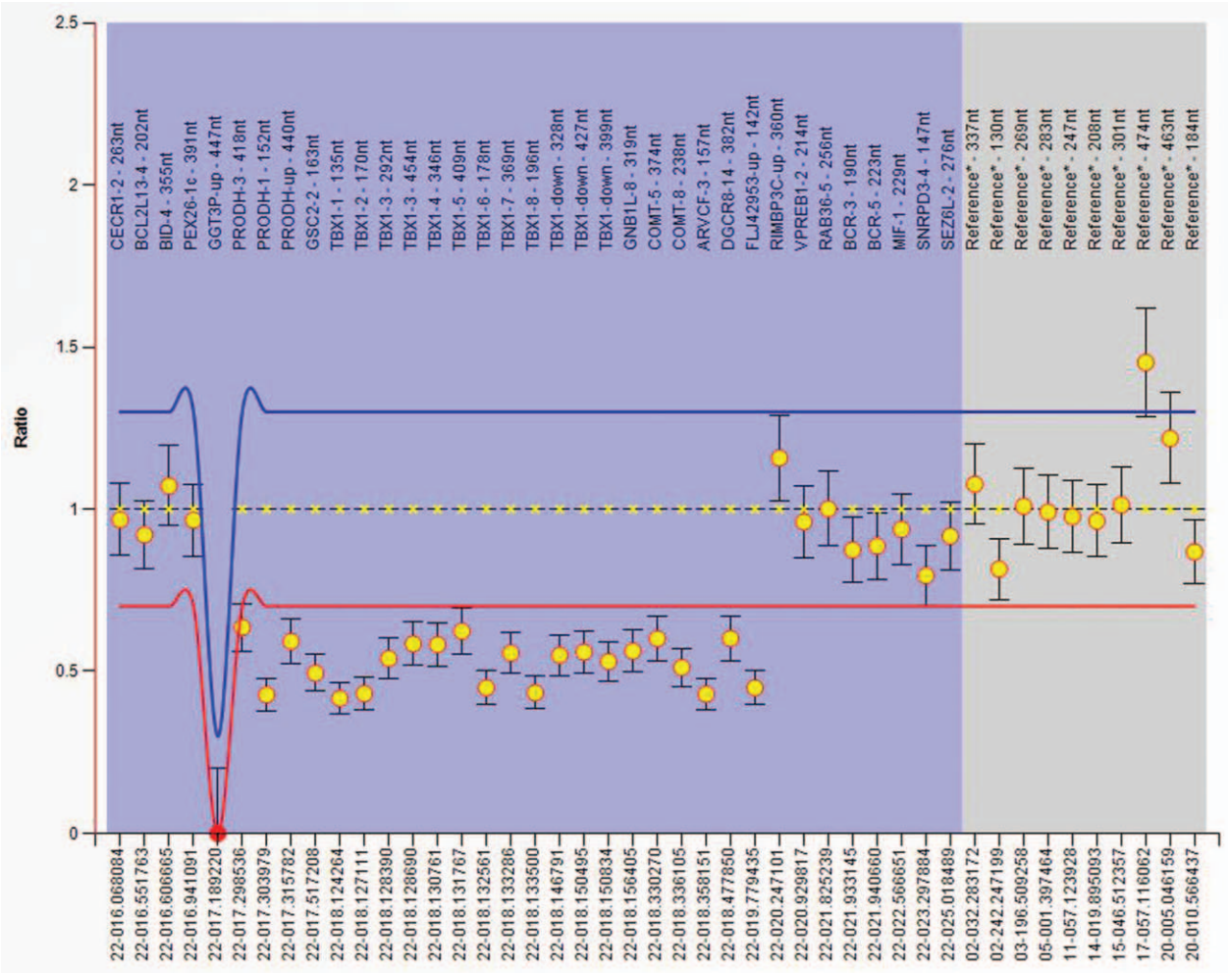

Figure 3. MLPA technique was used to detect the deletion of 22q11.2. (range: PR 0DH-FLJ42953).

22q11.2 deletion syndrome was confirmed (range, PR0DH-FLJ42953) (Fig. 3) at our hospital. The patient was diagnosed with pseudohypoparathyroidism because of his convulsions, hypocalcemia, hyperphosphatemia, normal PTH levels, and basal ganglia calcifications. The collection of human specimens was approved by the Second Affiliated Hospital of Nanchang University Human Research Ethics committee and written informed consent was obtained from participant. Because the participant was under the age of 16, their parents or legal guardians provided written, informed consent.

3. Discussion

Nephrotic syndrome is a glomerular disorder of childhood that causes proteinuria, hypoalbuminemia, and edema.[4] Our patient had 22q11.2 deletion syndrome, pseudohypoparathyroidism, convulsions, hypocalcemia, hyperphosphatemia, normal PTH levels, basal ganglia calcifications, congenital cardiovascular anomalies, and other phenotypes during childhood. Although hypocalcemia is a complication of nephrotic syndrome, renal dysfunction may also be caused by hypocalcemia.[5] He had abnormal facial features and speech and hypocalcemia, which are also characteristics of nephrotic syndrome. However, these characteristics have not been given enough attention by physicians; therefore, they can lead to the misdiagnosis of nephrotic syndrome. Hypocalcemia and vitamin D deficiency are associated with pseudohypoparathyroidism in children. If the patient is diagnosed with nephrotic syndrome, then oral hormone therapy is required for 9 months. Long-term treatment with hormone therapy will cause many complications; therefore, a clear diagnosis is very important. Our patient was first diagnosed with nephrotic syndrome because of the results of the examination performed at the local hospital; however, he had hypocalcemia, hyperphosphatemia, and normal PTH levels. After hormone and calcium therapy for 2 months, proteinuria and hypocalcemia still existed; therefore, the patient was referred to our hospital for treatment. Because he presented with lesions on multiple organs, multiplex ligation-dependent probe amplification was performed, which confirmed 22q11.2 deletion syndrome.

The phenotypic expression of 22q11.2 deletion syndrome has wide variability. Congenital heart defects, certain facial characteristics, immune deficiency due to thymic hypoplasia, cleft palate, velofacial dysfunction, hypocalcemia associated with hypoparathyroidism, and developmental and behavioral problems are the main characteristics associated with the syndrome.[3,6–8] 22q11.2

deletion syndrome could be found earlier if patients exhibit congenital cardiovascular anomalies coupled with other phenotypes during childhood. In our case, the diagnosis of 22q11.2 deletion syndrome was delayed because he did not present cardiovascular abnormalities, the typical facial appearance associated with the disorder, cleft palate, regurgitation, or symptoms of hypocalcemia during early infancy. Furthermore, hypoparathyroidism could not be observed. Unexpectedly, our patient exhibited pseudohypoparathyroidism, which was easily ignored by the clinician. In 1997, Craigen et al[9] reported a patient with microdeletion of 22q and pseudohypoparathyroidism, which may have been due to haploinsufficiency for a G protein; therefore, the identification of a contiguous deletion as the cause of pseudohypoparathyroidism was sought. Because of the association of 22q11 deletion syndrome with pseudohypoparathyroidism and hypocalcemia, this was not surprising. Therefore, patients with seizures were retroactively identified as having experienced documented hypocalcemia soon before those seizures.[10]

Pseudohypoparathyroidism is a rare heterogeneous genetic disorder characterized by resistance to the peripheral action of PTH. It was described by Cianferotti et al[11] as a syndrome characterized by short stature, round face, short neck, obesity, subcutaneous calcifications, shortened fourth metacarpals and metatarsals, and laboratory test results consistent with hypocalcemia, hyperphosphatemia, and increasing or normal PTH levels. Our case demonstrated a round face, short neck, hypocalcemia, hyperphosphatemia, normal PTH and alkaline phosphatase levels, and right basal ganglia calcifications. His Chvostek and Trousseau signs were positive. Therefore, the diagnosis of pseudohypoparathyroidism was considered.

Pseudohypoparathyroidism has 2 types (type I and type II) that are diagnosed according to whether cAMP could be normally synthesized by ectogenic PTH-stimulated kidneys. If the kidney can synthesize cAMP, then type II is considered. Type I has 3 subtypes (Ia, Ib, and Ic). Patients with pseudohypoparathyroidism type Ia have short stature, obesity, a round face, and a tendency for heterotopic ossification. Moreover, resistance to multiple hormones decreased erythrocyte G activity, and decreased cellular cAMP responses to PTH infusion exist in these patients.[12,13] Pseudohypoparathyroidism type Ib exhibits PTH resistance and normal erythrocyte G activity, but there is no abnormal phenotype. Pseudohypoparathyroidism type Ic exhibits resistance to diverse hormones in addition to PTH and includes abnormal phenotypes, but the erythrocyte G activity is normal. Although patients with type II have normal erythrocyte G activity and a normal cAMP response to PTH infusion, cAMP could not produce biological effects in cytoplasm.[12,13] Based on these standards, our case seemed to have type II.

Patients with pseudohypoparathyroidism usually require treatment with oral calcium supplements and 1, 25-dihydroxyvitamin D.[14] Because an increased PTH level is usually the most sensitive indicator of PTH resistance, asymptomatic patients with normal calcium and phosphate levels should also be treated to normalize PTH levels and prevent hyperparathyroid bone disease. It should be noted that the medical treatment for these abnormalities caused by this type of hormone resistance is currently the same as that for pseudohypoparathyroidism type I and pseudohypoparathyroidism type II.[15]

Positive findings for 22q11.2 deletion syndrome in our patient were delayed speech development due to velofacial dysfunction, recurrent croup attacks during early childhood due to latent hypocalcemia, and mild dysmorphic features. These findings indicated that 22q11.2 deletion syndrome presents a wide spectrum of clinical findings and that this diagnosis needs to be considered for all patients presenting with hypocalcemia, regardless of age.

4. Conclusion

The 22q11.2 deletion syndrome with pseudohypoparathyroidism is rare in children, and its phenotypic spectrum varies widely. We reported a case of delayed diagnosis of 22q11.2 deletion syndrome in a 14-year-old boy. He demonstrated nephrotic syndrome and subsequently underwent MPLA, which confirmed 22q11.2 deletion syndrome. When a patient has multiple deformities, even if pseudohypoparathyroidism has been diagnosed, 22q11.2 deletion syndrome should be considered. It is not impossible for 22q11.2 deletion syndrome to occur simultaneously with pseudohypoparathyroidism.

Acknowledgments

We thank Dr Xiaochun Cao for helpful collecting data during this study.

Author contributions

Conceptualization: Xi-Juan Liu.
Data curation: Xi-Juan Liu.
Formal analysis: Jingyu Jia.
Funding acquisition: Xi-Juan Liu.
Investigation: Xi-Juan Liu.
Methodology: Xi-Juan Liu, Chen Yan.
Project administration: Xi-Juan Liu.
Resources: Xi-Juan Liu.
Software: Jingyu Jia.
Supervision: Xi-Juan Liu.
Validation: Xi-Juan Liu.
Visualization: Xi-Juan Liu.
Writing – original draft: Xi-Juan Liu.
Writing – review & editing: Jingyu Jia.

References

[1] Tezenas Du Montcel S, Mendizabai H, Ayme S, et al. Prevalence of 22q11 microdeletion. J Med Genet 1996;33:719.
[2] Deng Y, Goodrich-Hunsaker NJ, Cabaral M, et al. Disrupted fornix integrity in children with chromosome 22q11.2 deletion syndrome. Psychiatry Res 2015;232:106–14.
[3] Ohi K, Hashimoto R, Yamamori H, et al. How to diagnose the 22q11.2 deletion syndrome in patients with schizophrenia: a case report. Ann Gen Psychiatry 2013;12:29.
[4] Aloni MN, Sysleyne LM, Ekulu PM, et al. The challenges of caring for children with nephrotic syndrome in a tertiary institution in the Democratic Republic of Congo. Acta Paediatr 2014;103:e365–9.
[5] Park SJ, Shin JI. Complications of nephrotic syndrome. Korean J Pediatr 2011;54:322–8.
[6] Greig F, Paul E, DiMartino-Nardi J, et al. Transient congenital hypoparathyroidism: resolution and recurrence in chromosome 22q11 deletion. J Pediatr 1996;128:563–7.
[7] Jyonouchi S, McDonald-McGinn DM, Bale S, et al. CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) syndrome and chromosome 22q11.2 deletion syndrome: a comparison of immunologic and nonimmunologic phenotypic features. Pediatrics 2009;123:e871–7.
[8] Benn P, Iyengar S, Crowley TB, et al. Pediatric healthcare costs for patients with 22q11.2 deletion syndrome. Mol Genet Genomic Med 2017;5:631–8.

[9] Craigen WJ, Lindsay EA, Bricker JT, et al. Deletion of chromosome 22q11 and pseudohypoparathyroidism. Am J Med Genet 1997; 72:63–5.
[10] Borders CB, Suzuki A, Safani D. Treatment of 22q11.2 deletion syndrome-associated schizophrenia with comorbid anxiety and panic disorder. Ment Illn 2017;9:7225.
[11] Cianferotti L, Brandi ML. Pseudohypoparathyroidism. Minerva Endocrinol 2018;43:156–67.
[12] Mantovani G, Spada A. Mutations in the Gs alpha gene causing hormone resistance. Best Pract Res Clin Endocrinol Metab 2006;20:501–13.
[13] Roberts TT, Khasnavis S, Papaliodis DN, et al. Spinal cord compression in pseudohypoparathyroidism. Spine J Off J North Am Spine Soc 2013;13:e15–9.
[14] Wang O, Xing XP, Meng XW, et al. Treatment of hypocalcemia caused by hypoparathyroidism or pseudohypoparathyroidism with domestic-made calcitriol: a prospective and self-controlled clinical trial. Chin Med J 2009;122:279–83.
[15] Li P, Huang L, Zhao Z, et al. Spinal-cord compression related to pseudohypoparathyroidism. J Clin Neurosci Off J Neurosurg Soc Australasia 2011;18:143–5.