Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Case Raport | Praca kazuistyczna
Pediatr Endocrino Diabetes Metab 2018;24,2:106-109
DOI: 10.18544/PEDM-24.02.0109

Oral prednisolone for management of persistent hypercalcemia after hypercalcemic crisis in the Williams-Beuren syndrome

Doustny prednizolon w leczeniu przewlekłej hiperkalcemii po przełomie hiperkalcemicznym w zespole Williamsa-Beurena

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Abstract
Hypercalcemia may occur in approximately 15% of children with the Williams-Beuren syndrome. The episodes of hypercalcemic crisis usually respond well to initial hyperhydration, loop diuretics and calcitonin, bisphosphonates, or subsequent dialysis. However, many patients suffer from recurrent or persistent hypercalcemia after the resolution of the hypercalcemic crisis. Although hypercalcemia in the Williams-Beuren syndrome is generally considered transient, it may last for several months, result in significant morbidity, and compromise physical growth. There are no guidelines for the management of persistent or recurrent hypercalcemia in patients with the Williams-Beuren syndrome. In this report, we describe our experience of conducting oral corticosteroid therapy in a child with the Williams-Beuren syndrome who continued to have hypercalcemia after the resolution of the hypercalcemic crisis.
Keywords
Williams Beuren syndrome, hypercalcemic crisis, persistent hypercalcemia, treatment, prednisolone

Streszczenie
Hiperkalcemia może wystąpić u około 15% dzieci z zespołem Williamsa-Beurena. Incydent hiperkalcemicznego przełomu zazwyczaj dobrze odpowiada na leczenie za pomocą nawodnienia, diurtetyków pętlowych, kalyctonimy, bifosfonianów czy późniejszej dializy. Jednak wielu pacjentów, po przebyciu przełomu hiperkalcemicznego, cierpi z powodu nawracającej hiperkalcemii. Chociaż uważa się, że hiperkalcemia w zespole Williamsa-Beurena ma postać przejściową, może jednak trwać kilka miesięcy i prowadzić do istotnego wpływu na przebieg choroby i rozwój fizyczny dziecka. Nie istnieją wytyczne co do postępowania w przetrwałej lub nawracającej hiperkalcemii u pacjentów z zespołem Williamsa-Beurena. W tym doniesieniu, opisujemy nasze doświadczenia z zastosowaniem terapii kortykosteroidami u dziecka z zespołem Williamsa-Beurena, u którego po przebyciu przełomu hiperkalcemicznego utrzymywała się nadal hiperkalcemia.
Słowa kluczowe
zespół Williamsa-Beurena, przełom hiperkalcemiczny, przetrwała hiperkalcemia, leczenie, prednizolon

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Received: 13.06.2018
Accepted: 20.07.2018
Conflict of interests: none declared.

Introduction

The Williams-Beuren syndrome (WBS, OMIM 194050) is a rare multisystemic genetic disorder caused by a microdeletion of chromosome 7q11.23 [1]. Patients with WBS have distinctive facial dysmorphism, congenital heart disease, specific neurocognitive profile, growth retardation, and variable abnormalities of genitourinary, ophthalmological, skeletal and endocrine systems [1]. Several endocrine problems, such as short stature, hypothyroidism, hypopituitarism, pubertal disorders, lipid abnormalities, glucose intolerance, impaired bone metabolism, and hypercalcemia have been described in WBS [2,3]. Although most patients with WBS may have higher plasma calcium levels than controls, actionable hypercalcemia occurs infrequently [4]. The manifestations of hypercalcemia in WBS are usually mild and non-life threatening, but the consequences, such as dehydration, hypercalciuria, nephrocalcinosis, poor oral intake, and growth impairment may result in significant morbidity [4]. The management of acute severe hypercalcemia usually involves initial treatment using hyperhydration and loop diuretics, and steroids, calcitonin, bisphosphonates and dialysis if serum calcium concentrations fail to drop [4,5]. With the treatment of acute hypercalcemic episode, the serum calcium levels usually remain below the actionable range but some patients may suffer from recurrences and chronic hypercalcemia [4,6]. There is scarce information on the treatment of chronic hypercalcemia in WBS although most patients are managed with restriction of dietary calcium and vitamin D intake below the recommended daily intake (RDI) similar to other disorders with the risk of hypercalcemia with RDI doses of calcium and vitamin D [7]. We report an infant with WBS who showed a recurrence of hypercalcemia after the treatment of the hypercalcemic crisis and was successfully managed with oral glucocorticoid therapy along with the increase in free water access and restriction of dietary calcium and vitamin D.

Case report

An 8-month-old boy was referred to us for poor weight gain, developmental delay, constipation, increased oral water intake, and increased frequency of urination (up to 20 times per day) since the time he was 3 months old, and irritability for the last one month. There was no history of fever or seizures. There was no history suggestive of similar illness or an endocrine disorder in the family. He was born at term by caesarean section for twin pregnancy and had no perinatal problems. The birth weight was 2.5 kg (the other twin weighed 3.5 kg). He was on mixed feeds with breast milk, formula milk and cow's milk. He had received oral calcium (25 mg/kg/day) and cholecalciferol supplementation (400 IU/day) respectively until he was 3 months old. The routine biochemistry measurements performed elsewhere showed increased serum calcium levels, and he was referred to our endocrine unit for etiological work-up.

Physical examination showed distinct facial features suggestive of WBS, such as the broad forehead, elongated face, long philtrum, depressed nasal bridge, full cheeks, thick lower lip, and right ear pit. The vital parameters were normal. His weight was 5.0 kg (-3.5 z-score, standard WHO growth charts) (-2.0 z-score, William's growth charts), length 59.5 cm (-3.8 z-score, standard WHO growth charts) (-2.0 z-score, William's growth charts), head circumference 41.0 cm (-3.3 z-score, standard WHO growth charts) (-2.0 z-score, William's growth charts) and body mass index 14.1 kg/m^2 (-2.3 z-score, standard WHO growth charts). The systemic examination was unremarkable.

Laboratory investigations revealed normal hematological parameters. Serum trioidothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH) levels were 1.01 ng/mL (normal range 0.2-2.0 ng/mL), 3.96 μg/dL (normal range, 4.8-12.7 μg/dL) and 6.06 μIU/mL (normal range, 0.27-4.2 μIU/mL) respectively, suggestive of primary hypothyroidism. Ultrasonogram of thyroid showed that the gland was within the norm. Echocardiography was also normal. The results of the assessment of hearing were within the norm. Serum and lipase levels were 50 U/L and 10 U/L respectively. The ultrasonogram of abdomen showed bilateral medullary nephrocalcinosis and normal other internal organs. The blood and urine pH were 7.38 and 7.0 respectively. Urine osmolality was 350 mOsm/kg. Fluorescence in situ hybridization (FISH) using LSI ELN spectrum orange/LSI D7S486, D7S522 spectrum green probes revealed a deletion on chromosome 7 (q11.23q11.23)(ELN/LIMK1) consistent with the diagnosis of WBS.

The biochemistry parameters related to calcium metabolism during and after the hospitalization for the hypercalcemic crisis are shown in Table 1. The child was administered hyperhydration at 150% of normal daily fluid requirements along with furosemide (2 mg/kg/dose, 6 hourly). However, serum and ionized calcium concentrations remained high after 2 days of forced diuresis. On day 3 of the hospitalization, the child was given subcutaneous calcitonin (4 IU/kg/dose) 12 hours apart in addition to hyperhydration and diuretics. Serum calcium fell from 14.1 to 12.7 mg/dL and remained between 12.7 to 13.1 mg/dL until day 6. On day 7, serum calcium again rose to 15.0 mg/dL and required two additional doses of calcitonin. The child was initiated on oral prednisolone (1 mg/kg/day) on day 10 of hospital stay, and discharged on day 12 with advice on calcium and vitamin D restriction and free oral water intake. At his first follow-up visit 2 weeks later, serum calcium was still high for which the dose of prednisolone was increased to 2 mg/kg/day. Considering the transient nature of hypercalcemia in WBS, tapering of prednisolone was started after one month of the administration of the full dose. The child suffered a recurrence of hypercalcemia and the prednisone dose had to be increased again to 2 mg/kg/day (Table 1). The tapering and complete discontinuation of prednisolone after a month of the administration of the full dose were achieved over the next month. Free water intake was continued with further plan to introduce vitamin D and calcium in smaller doses. At his latest follow-up at 1 yr of chronological age, his weight was 7.0 kg (-3.0 z-score, standard WHO growth charts), length 68.0 cm (-3.1 z-score, standard WHO growth charts) and head circum-

Table I. Biochemical parameters during and after hospitalization

Variable	During hospital stay												During follow up visits				
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	2 wk	6 wk	8 wk	12 wk	16 wk
S. Calcium (mg/dL)	14.9	14.1	12.7	12.1	12.7	12.9	13.1	15.0	12.4	11.9	11.3	10.8	14.0	12.4	14.2	11.5	10.8
Ionized Calcium (mmol/L)	1.14			1.04				1.73	0.96			1.15					
S.Phosphate (mg/dL)	4.6	4.5	4.3	3.3	4	3.3	3.3	1.9	4.3	3.9	4	3.8				5.2	
S. ALP (IU/L)	143	131	128	137	126	133	129	118								124	
S. Magnesium (mg/dL)		2.3					2.1				2.3						
S. PTH (pg/mL)	5.7									18.3						36.4	
25-hydroxy-vitamin D (ng/mL)	52.1									41.0						32.2	
1,25-dihydroxy-vitamin D(pg/mL)	86.4															62.5	
Urine ca:cr	3.8								1.2							0.4	

ference 43.0 cm (-2.3 z-score, standard WHO growth charts). An informed consent from the parents was obtained for the publication of the case report.

Discussion

Hypercalcemia is commonly seen in WBS patients with a combined prevalence of about 15% [4]. However, actionable hypercalcemia occurs infrequently and usually shows a bimodal age distribution: infancy and adolescence, or adulthood [4]. Although hypercalcemia is generally considered transient during infancy, it may last for several months and result in significant morbidity [4,6]. The usual consequences of hypercalcemia such as dehydration, irritability, decreased oral intake, polyuria and polydipsia result in failure to thrive and contribute to an already compromised growth in WBS [4]. The severity of growth failure may be similar to that of children with severe growth hormone deficiency or diabetes insipidus [8,9]. Additionally, serious dysfunction of several organ systems as seen in hypercalcemia associated with other disorders may occur [7]. In particular, the effects of chronic hypercalcemia and hypercalciuria on the renal system as seen in our patient need consideration. Therefore, it seems reasonable to monitor and keep the serum calcium levels to near normal levels in follow-up [4]. There are, however, no clear guidelines on how to manage persistent or recurrent hypercalcemia in WBS. Although patients in the hypercalcemic crises seem to respond well to several calcium lowering drugs, a long-term use of these agents is generally avoided [4,10]. A closely supervised reduction in the intakes of calcium and vitamin D as well as free water intake may lower serum calcium levels in most but not all patients with WBS [6,11]. Considering that our patient exhibited severe growth failure, nephrocalcinosis and the recurrence of hypercalcemia, we aimed to treat him with steroid therapy which had previously been used to treat acute hypercalcemia in WBS as well as chronic hypercalcemia due to other conditions in children [4]. With this therapy, along with calcium and vitamin D restriction, a gradual amelioration of symptoms and reduction of serum calcium levels were achieved in our patient.

Although the exact mechanism of hypercalcemia in WBS is unknown, a common finding in patients with WBS is an increased sensitivity to vitamin D and enhanced calcium absorption from the gut, possibly due to decreased ability of ligand-bound Vitamin D receptor (VDR) to mediate transrepression of the 1α-hydroxylase gene, CYP27B1 [10]. This defect appears to be due to haploinsufficiency of the Williams syndrome transcription factor (WSTF) located within the deleted region of chromosome 7q11.23 [10]. The VDR interacts with a multifunctional chromatin remodeling complex called WINAC through WSTF. Therefore, the loss of WSTF prevents 1,25-dihydroxyvitamin D bound VDR-induced transrepression of CYP27B1 [12]. Serum 1,25-dihydroxyvitamin D levels are usually elevated in WBS children despite hypercalcemia and result in an increased calcium absorption from the gut [4]. Steroids inhibit 1-α-hydroxylase mediated conversion of 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D thus reducing intestinal calcium absorption [4]. Therefore, the use of corticosteroids appears to be a reasonable choice for the treatment of hypercalcemia in WBS. In our patient, the gradual decrease of serum concentrations of 1,25-dihydroxyvitamin D after starting prednisolone probably indicates a mechanism of 1-α-hydroxylase inhibition by corticosteroids.

We chose a low initial dose of prednisolone to avoid significant effects on growth. However, the dose had to be increased due to the recurrence of actionable hypercalcemia which occurred twice. We stopped prednisolone when calcium concentrations were consistently below the actionable range defined as plasma Ca >0.5 mg/dL above pediatric-adjusted hypercalcemia norms [4]. However, we plan to continue with free water intake and supervised vitamin D and calcium supplementation as recommended [4]. In view of non-availability of approved guidelines, we propose that short-term oral prednisolone may be used for the treatment of persistent and recurrent hypercalcemia in WBS.

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