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IDIOPATHIC INFANTILE HYPERCALCEMIA – CASE REPORT

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Abstract

Idiopathic Infantile Hypercalcemia (IIH) is a rare genetic disease which cardinal features is failure to thrive, polyuria, dehydration, vomiting, seizures, lethargy, comma and if unrecognized and untreated may result in death.

Laboratory investigations show hypercalcemia, hypercalciuria, elevated values of 1, 25 (OH) D3 and suppressed levels of parathormon. Ultrasound study usually reveals bilateral medullary echogenicity typical for nephrocalcinosis. Emergency treatment consists from large hydration, prednisolone, calcitonin and biphosphonates, which were used with success. In this report we present a 6 month old female infant who came to our attention due to growth delay as a consequence of polyuria, vomiting and poor apetite.

Dietary management with withdrawal of vitamin D and reduction of calcium intake significantly improved the general health status and normalized the serum biochemistry. The diagnosis was established with mutational analysis of the *CYP24A1* gene.

Key words: idiopathic infantile hypercalcemia, *CYP24A1*, vitamin D, nephrocalcinosis.

Introduction

The cardinal features of Idiopathic Infantile Hypercalcemia (IIH) are failure to thrive, polyuria, dehydration, vomiting, seizures, lethargy and in most severe cases coma and death [1, 2, 3, 4]. Laboratory studies show hypercalcemia, hypercalciuria, elevated levels of 1,25 (OH) D3 and suppressed levels of parathormon.

Often there is diagnostic confusion with William Beuren syndrome which has similar clinical and laboratory features, but these patients have typical dysmorphic features (elfin face).

The infants with IIH are sensitive to regular prophylactic doses of vitamin D. Therefore vitamin D prophylaxis and supplements should be immediately withdrawn in order to prevent hypercalcemia and nephrocalcinosis. The mild clinical fcatures in some infants may lead to delay of the diagnosis. In this report work we present a 6 month old female infant whose clinical diagnose of IIH was genetically confirmed with the mutational analysis of the *CYP24A1* gene.

Case report

A 6 month old female infant from Albanian ethnicity attracted the medical attention of her pediatrician due to failure to thrive, vomiting, dehydration and poor appetite. Her growth parameters were as follows: weight 4.4 kg (<3rd percentile), length: 56 cm (5th percentile). The laboratory parameters showed normal hematology parameters, no disturbances in acid base status and normal anion gap (14.0 mmol/l).

Biochemical analysis: Glucose 4.5 mmol/l, Urea 4.2 mmol/l, Na 138 mmol/l, K 4.8 mmol/l, Cl 104 mmol/l, Ca 3.89 mmol/l, Mg 0.7 mmol/l, Cholesterol 3.1 mmol/l, Tryglicerides 0.77 mmol/l, uric acid 242 umol/l, total proteins 62 g/l, Albumen 42 g/l, AST 45 U/l, ALT 41 U/l, LDH 695 U/l. ALKP 136 U/l, CK 24 U/l, Total bilirubin 3 umol/l, PTH extremely low < 3 pg/ml; Urine: Glucose <0.6 mmol/l, Urea 50.1 mmol/l, Na 18 mmol/l, K 12.6 mmol/l; Ca 2.25 mmol/l, Mg 0.8 mmol/l, uric acid 1160 mmol/l, creatinine 0.85 mmol/l, osmolality 66.7 m Osm/kg. Calcium/creatinine ratio was 2.68mmol/mmol(normal<2.2).

Kidney ultrasonography showed bilateral medullary hyperechogeneicity consistent with nephrocalcinosis (Fig 1).

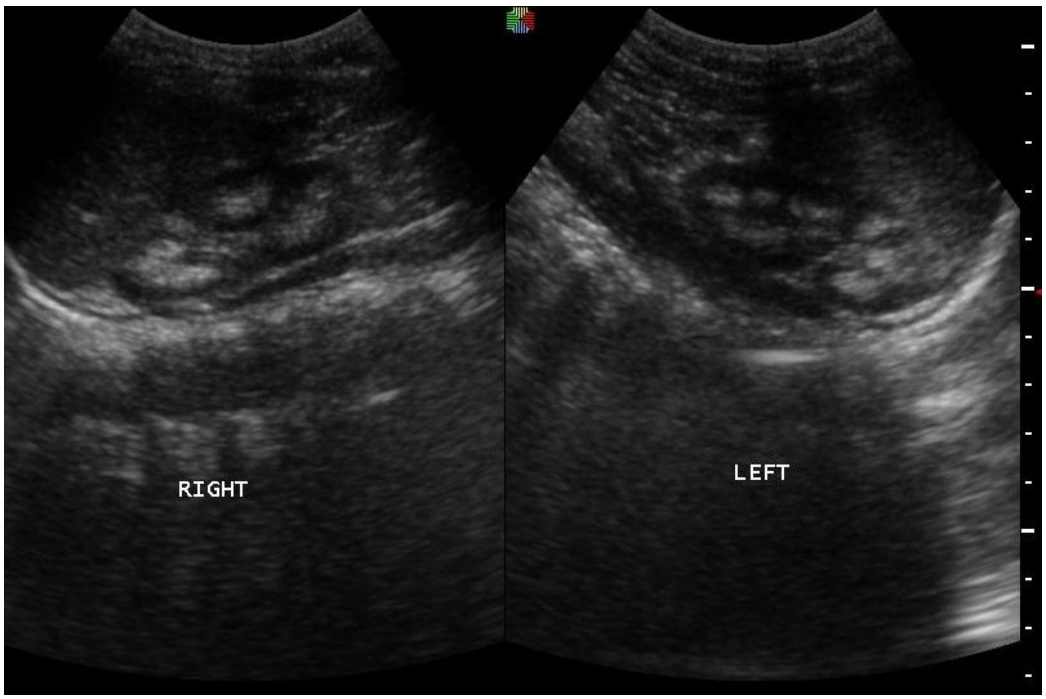

Figure 1. Bilateral medullary nephrocalcinosis

The both parents and sister had normal kidney ultrasound pattern. The vitamin D prophylaxis and all supplements containing vitamin D were immediately withdrawn and calcium intake reduced. The baby was fed with a special milk formula.

Two months later the baby was again seen at the outpatient Clinics and showed marked improvement of the growth and biochemical parameters; the weight of the baby was 7350 gr and length: 71 cm. Serum calcium was 3.2 mmol/l, but parathormon was still suppressed at (PTH <3.0 pg/ml). Urine calcium/creatinine ratio was within referent values.

At the age of 8.5 months her weight was 10.2 kg, and length: 78 cm. This time her serum calcium was within referent values 2.62 mmol/l, but PTH < 3 pg/ml. The mutational analysis revealed typical homozygous Central European mutation E143del in *CYP24A1* gene. The both parents and healthy sister were heterozygous carriers of this mutation.

Discussion

The ulstrasound pattern of bilateral medullary hyperechogenecity is the result of calcium oxalate deposits which result in neprocalcinosis. Rarely medulary hyperechigenecity is due to urate deposits. In our patient uric acid nephropathy was excluded based on normal serum urate levels. Nephrocalcinosis is the challenging item for nephrologist due to the very heterogeneous etiology.

The most common etiological factor is distal renal tbular acidosis (DRTA) which may be complete (overt) or incomplete. [5,6]. We easily excluded DRTA since our patient had normal plasma bicarbonate and low urine pH <5.5

Hypercalcemia and low PTH levels guided us to the diagnosis of idiopathic infantile hypercalcemia. Generaly idiopathic infantile hypercalcemia (IIH) presents early in the infancy with failure to thive, dehydration crisis due to polyuria, constipation, hypotonia, seizures, comma and in most severe cases with death if not recognized and treated promptly.

It is very important to differentiate IIH from William Beuren syndrome which has similar renal phenotype (medullary nephrocalcinosis, hypercalcemia, hypercalciuria, suppressed PTH).

Children with Williams Beuren syndrome have typical facial dysmorphy (elfin face), congenital cardiopathy and intellectual disability. The genetic basis of this syndrome has already been established, that is microdeletion of the 7th chromosome (7q11.23) which encompass elastin and additionally 27 genes [7, 8, 9]. The pathophysiology and genetics of IIH had been confused for many decades until group from Muenster (Germany) published report in New England Journal of Medicine in 2011 and found that majority of patients with IIH had mutation *CYP24A1* gene.

These gene codes 24 hydroxylase, an enzyme involved in degradation pathway of the vitamin D metabolism. To validate their finding they tested adult patients from former German Democratic Republic who had been treated in infancy with high prophylactic parenteral dosis of cholecalciferol (2 million units during the first two years) and who had developed signs of vitamin D toxicity. As expected these patients carried *CYP24A1* mutation [10].

IIH was considered as exclusively infantile disease but further reportes described adult patients with idiopathic calcium oxalate stones or unclear nephrocalcinosis who also had mutations in the *CYP24A1* gene.

Interestingly they had variable clinical presentation – with hypercalciuria, normal serum calcium levels or transitory mild hypercalcemia, but PTH values were persistently low [11, 12].

Our patient was found to have bilateral medullary nephrocalcinosis. Her growth and health status during the first year of life were disturbed due to polyuria, vomiting and poor apetite. Withdrawal of vitamin D and reduction of calcium intake had benefitary effect on the general health status and normalization of the serum biochemistry.

In patients with severe clinical presentation one should implement large hydration, prednisolone, calcitonin and biphosphonates, which were used with success [13, 14, 15].

Another interesting approach is treatment with ketoconazole which reduces 1, 25 (OH) D3 levels and corrects hypercalcemia in primary hyperparathyroidism and granulomatosus disorders [16]. Beside low calcium diet and avoidance of Vitamin D supplements, there is recommendation for sun protection, since inactivation of Vitamin D compounds seems to be the primary problem in patients with IIH and *CYP24A1* gene mutations [17, 18].

Patients who suffered from IH have a greater risk of progressive chronic kidney disease and nephrocalcinosis. In a study from Poland the long-term outcome was assessed in 18 patients with an average age of 23.8 years (age range 2-34)[19].

The average glomerular filtration rate (GFR) was 72 mL/min/1.73 m2 (range 15-105). Two patients developed ESRD and underwent renal transplantation. A GFR <90 mL/min/1.73 m2 was found in 14 patients (77%), whereas a GFR <60 mL/min/1.73 m2 was seen in 5 patients (28%), including 2 adults after renal transplantation. Three of 18 patients still had serum calcium levels >2.6 mmol/L. A renal ultrasound revealed nephrocalcinosis in 16 of 18 (88%) patients, however, mild hypercalciuria was detected in only one subject.

In our patient the diagnosis was confirmed with the analysis of the *CYP24A1* gene (homozygous E141del mutation). This mutation was reported in the infantile form of the disease by Schlingmann et al. and is typical for the Central and Estearn European populations [10, 20, 21].

Genetic diagnosis is important to confirm the clinical diagnosis, for genetic counselling and for prenatal or postnatal diagnosis in next pregnancies in order to implement appropriate dietary measures in homozygous mutation carriers.

References:

1. Fencl F, Bláhová K, Schlingmann KP, Konrad M, Seeman T.Severe hypercalcemic crisis in an infant with idiopathic infantile hypercalcemia caused by mutation in CYP24A1 gene. Eur J Pediatr. 2013; 172:45-9
2. Zajadacz B, Juszkiewicz A. Nephrocalcinosis in a 2-month-old girl suffering from a mild variant of idiopathic infantile hypercalcemia. Wiad Lek. 2004;57:710-2.
3. Pronicka E, Rowińska E, Kulczycka H, Lukaszkiewicz J, Lorenc R, Janas R. Persistent hypercalciuria and elevated 25-hydroxyvitamin D3 in children with infantile hypercalcaemia. Pediatr Nephrol. 1997; 11:2-6.
4. Gut J, Kutílek Š. Idiopathic infantile hypercalcaemia in 5-month old girl. Prague Med Rep. 2011; 112:124-31
5. Dinour D, Beckerman P, Ganon L, Tordjman K, Eisenstein Z, Holtzman EJ. Loss-of-function mutations of CYP24A1, the vitamin D 24-hydroxylase gene, cause long-standing hypercalciuric nephrolithiasis and nephrocalcinosis. J Urol. 2013; 190:552-7.
6. Kenny J, Lees MM, Drury S, Barnicoat A, Van't Hoff W, Palmer R, Morrogh D, Waters JJ, Lench NJ, Bockenhauer D. Sotos syndrome, infantile hypercalcemia, and nephrocalcinosis: a contiguous gene syndrome. Pediatr Nephrol. 2011; 26:1331-4
7. Udwin O. A survey of adults with Williams syndrome and idiopathic infantile hypercalcaemia. Dev Med Child Neurol. 1990; 32:129-41.
8. Euteneuer J, Carvalho CM, Kulkarni S, Vineyard M, Grady RM, Lupski JR, Shinawi M.Molecular and phenotypic characterization of atypical Williams-Beuren syndrome. Clin Genet. 2014; 86:487-91
9. Leme DE, Souza DH, Mercado G, Pastene E, Dias A, Moretti-Ferreira D.Assessment of clinical scoring systems for the diagnosis of Williams-Beuren syndrome. Genet Mol Res. 2013; 12:3407-11.
10. Schlingmann KP, Kaufmann M, Weber S et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. N Engl J Med. 2011; 365:410-21.
11. Dauber A, Nguyen TT, Sochett E, Cole DE, Horst R, Abrams SA, Carpenter TO, Hirschhorn JN. Genetic defect in CYP24A1, the vitamin D 24-hydroxylase gene, in a patient with severe infantile hypercalcemia. J Clin Endocrinol Metab. 2012; 97:E268-74.
12. Jones G, Prosser DE, Kaufmann M. 25-Hydroxyvitamin D-24-hydroxylase (CYP24A1): its important role in the degradation of vitamin D. Arch Biochem Biophys. 2012; 523:9-18.
13. Mizusawa Y, Burke JR. Prednisolone and cellulose phosphate treatment in idiopathic infantile hypercalcaemia with nephrocalcinosis. J Paediatr Child Health. 1996; 32:350-2.
14. Shimizu H, Kodama S, Takeuchi A, Matui T, Nakao H, Sakurai T, Kobayashi T. Idiopathic infantile hypercalcemia discovered in the newborn period. Acta Paediatr Jpn. 1994; 36:720-3.
15. Alon U, Berkowitz D, Berant M. Idiopathic infantile hypercalcemia: rapid response to treatment with calcitonin. Child Nephrol Urol. 1992;12:47-50.
16. Meusburger E, Mündlein A, Zitt E, Obermayer-Pietsch B, Kotzot D, Lhotta K. Medullary nephrocalcinosis in an adult patient with idiopathic infantile hypercalcaemia and a novel CYP24A1 mutation. Clin Kidney J. 2013; 6:211-215.
17. Dinour D, Davidovits M, Aviner S, Ganon L, Michael L, Modan-Moses D, Vered I, Bibi H, Frishberg Y, Holtzman EJ. Maternal and infantile hypercalcemia caused by vitamin-D-hydroxylase mutations and vitamin D intake. Pediatr Nephrol. 2015; 30:145-52.
18. Castanet M, Mallet E, Kottler ML. Lightwood syndrome revisited with a novel mutation in CYP24 and vitamin D supplement recommendations. J Pediatr. 2013; 163:1208-10.
19. Janiec A, Halat-Wolska P, Obrycki Ł, Ciara E, Wójcik M, Płudowski P, Wierzbicka A, Kowalska E, Książyk JB, Kułaga Z, Pronicka E, Litwin M. Long-term outcome of the survivors of infantile hypercalcaemia with CYP24A1 and SLC34A1 mutations. Nephrol Dial Transplant. 2020 Oct 25:gfaa178. doi: 10.1093/ndt/gfaa178. Online ahead of print.
20. Streeten EA, Zarbalian K, Damcott CM. CYP24A1 mutations in idiopathic infantile hypercalcemia. N Engl J Med. 2011; 365:1741-2;

21. Wolf P, Müller-Sacherer T, Baumgartner-Parzer S, Winhofer Y, Kroo J, Gessl A, Luger A, Krebs M. A Case of "Late-Onset" Idiopathic Infantile Hypercalcemia Secondary to Mutations in the CYP24A1 Gene. Endocr Pract. 2014; 20:e91-5.