Five years results after intrafamilial kidney post-transplant in a case of familial hypomagnesemia due to a claudin-19 mutation

Resultado cinco anos pós-transplante renal intrafamiliar em um caso de hipomagnesemia familiar devido a mutação da claudina-19

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Abstract

Introduction: Familial Hypomagnesaemia with hypercalciuria and nephrocalcinosis, with severe ocular impairment secondary to claudin-19 mutation, is a rare recessive autossomic disorder. Its spectrum includes renal Mg^{2+} wasting, medullary nephrocalcinosis and progressive chronic renal failure in young people. **Objective:** To report a case of kidney transplantation father to daughter in a familial occurrence of severe bilateral nephrocalcinosis associated with ocular impairment in a non-consanguineous Brazilian family, in which two daughters had nephrocalcinosis and severe retinopathy. **Methods:** The index case, a 19 years-old female, had long-lasting past medical history of recurrent urinary tract infections, and the abdominal X-ray revealed bilateral multiple renal calcifications as well as ureteral lithiasis, and she was under haemodialysis. She had the diagnosis of retinitis pigmentosa in the early neonatal period. The other daughter (13 years-old) had also nephrocalcinosis with preserved kidney function, retinopathy with severe visual impairment, and in addition, she exhibited hypomagnesaemia = 0.5 mg/dL and hypercalciuria. The other family members (mother, father and son) had no clinical disease manifestation. Mutation analysis at claudin-19 revealed two heterozygous missense mutations (P28L and G20D) in both affected daughters. The other family members exhibited mutant monoallelic status. In despite of that, the index case underwent intrafamilial living donor kidney transplantation (father). **Conclusion:** In conclusion, the disease was characterized by an autosomal recessive compound heterozygous status and, after five years of donation the renal graft function remained stable without recurrence of metabolic disturbances or nephrocalcinosis. Besides, donor single

Resumo

Introdução: Hipomagnesemia familiar com hipercalciúria e nefrocalcinose, com grave envolvimento ocular, por mutação no gene da claudina-19, é uma doença rara autossômica recessiva. Seu espectro inclui perda renal de magnésio, nefrocalcinose medular e doença renal progressiva em crianças e adolescentes. **Objetivo:** Relatar um caso de transplante renal pai para filha em uma ocorrência familiar de nefrocalcinose bilateral grave associada com comprometimento ocular em uma família brasileira não consangüínea, na qual duas filhas apresentavam nefrocalcinose e retinopatia severa. **Métodos:** O caso índice, uma mulher de 19 anos de idade, tinha longa história pregressa de infecção urinária de repetição, o raio-X abdominal revelava calcificações renais múltiplas bilaterais, bem como litíase ureteral, e estava sob hemodiálise. Havia um diagnóstico prévio de retinite pigmentosa no período neonatal precoce. A outra filha (13 anos de idade) também apresentava nefrocalcinose com função renal preservada, retinopatia com grave deficiência visual, e além disso, ela exibia hipomagnesemia = 0,5 mg/dL e hipercalciúria. Os outros membros da família (mãe, pai e filho) não tinham nenhuma manifestação clínica da doença. A análise mutacional no gene da claudin-19 revelou duas mutações heterozigotas (P28L e G20D) em ambas as filhas afetadas. Os outros membros da família apresentavam estado mutante monoalélico. Apesar disso, o caso índice foi submetido a transplante de rim com doador vivo intrafamiliar (pai). **Conclusão:** Em conclusão, a doença foi caracterizada por um estado heterozigoto recessivo composto autossômico e após cinco anos de doação a função do enxerto renal manteve-se estável, sem recidiva de distúrbios metabólicos ou nefrocalcinose. Além disso, a homeostasia do Mg^{2+} e Ca^{2+}

kidney Mg^{2+} and Ca^{2+} homeostasis associated to monoallelic status did not affect the safety and the usual living donor post-transplant clinical course.

Keywords: calcium metabolism disorders; genetic diseases, inborn; kidney transplantation.

associado ao estado monoalélicos do doador e seu rim único não afetou a segurança da doação intervivos e o curso clínico usual pós-transplante.

Palavras-chave: distúrbios do metabolismo do cálcio; doenças genéticas inatas; transplante de rim.

Introduction

Familial Hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal-recessive inherited disorder and its phenotypic spectrum includes renal wasting of magnesium and calcium with medullary nephrocalcinosis, and progressive renal failure which causes end-stage renal disease often during adolescence or young adult age.[1] FHHNC is caused by mutation in the claudin-16 gene located on chromosome 3, but now we can also recognize another similar disorder caused in another tight junction gene located on chromosome 1, that encodes claudin-19, distinguished by the association of severe ocular impairment, the so called FHHNC with severe ocular impairment.[2-6] Some series have identified groups of patients, particularly when caused to mutation on claudin-16, and they have been followed in evolution, genotyping correlation and progression to end stage renal disease, but a systematic analysis in relation to kidney transplantation is not yet well established.[7-9] Besides, there is a possible specific role to the new described mutant alleles to claudin-19 and its interaction with claudin-16.[6,10] In this report, we present a non-consanguineous Brazilian family having two daughters (13 and 19 years-old) with nephrocalcinosis and severe retinopathy, being the oldest one under haemodialysis due to end stage renal disease. Mutation analysis at claudin-19 revealed two heterozygous missense mutations (P28L and G20D) in both affected daughters. The other family members exhibited mutant monoallelic status. In despite of that, the oldest girl underwent a kidney transplantation having her father as the kidney donor.

Case report

A 19 years-old girl was diagnosed with uremic symptoms and underwent immediately at haemodialysis by a non-cuffed right femoral venous catheter. She had a history of repeated urinary tract infection episodes. An abdominal X-ray revealed bilateral renal calcifications and a 3 cm calculus near the uretero-vesical junction. Serologic tests to HIV, HCV and HBV were negative. She presented horizontal nystagmus and the mother reported a diagnosis of retinitis pigmentosa in the early neonatal period. Renal ultrasound revealed medullary nephrocalcinosis and chronic contracted kidneys.

At the same time, we evaluated the almost blind youngest 13 years-old daughter, who had the same diagnosis of retinitis pigmentosa and a medical past of several seizure episodes in the first two years of life, according to the mother. Renal ultrasound showed severe medullary nephrocalcinosis either, but presenting normal renal function (serum creatinine = 1.1 mg/dL). Surprisingly, she had consistent hypomagnesaemia confirmed at different evaluation points. Besides, the biochemical fluid analysis revealed hypercalciuria, mild hyperparathyroidism and high uric acid serum level, mild proteinuria, and urine sediment compatible with tubule-interstitial nephritis with no glomerular haematuria by phase microscopy. Arterial blood gas analysis was normal. Direct measurement of 12 hours fasting urine pH by using potentiometer were consitently normal associated to no potassium or chloride disturbances in all family until the end of study. Past medical history, physical and complementary exams in the remaining family members was usual. The parents are unrelated. A genetic disease hypothesis was made and genetic testing was performed to clarify its etiopathology.[6] In both affected daughters, two heterozygous missense mutations were detected, namely G20D and P28L. The G20D mutation has been often described in FHHNC patients of Hispanic origin. The second mutation inherited from the father was identified as a new mutation located in the first transmembrane domain of claudin-19 (P28L).[6]

The index case, the oldest daughter, underwent kidney transplantation having the father as the donor. The immunosuppressive scheme consisted of prednisone, mycophenolate mofetil and cyclosporine,

because of laboratorial blood testing availabilities. The post-operative period was complicated by acute rejection and by urinary fistula solved by intravenous pulses of corticoid and further surgical procedures, respectively. Since then, the patient routine report has no relevant incurrence except by the change of cyclosporine to sirolimus at the end of the first year, because of a light nephrotoxicity.

After five years of follow-up the renal graft function has remained stable and the metabolic ionic dislturbances observed prior to the transplantation achieved normal levels. In special, there were no disturbances in the magnesium and calcium homeostasis in both recipient and donor, in spite of the father be a carrier of a mutant allele. Annually renal graft post-transplant ultrasound has not revealed any evidence of nephrocalcinosis until the time of this report, and the renal function has been maintained stabilized (serum creatinine = 1.2 mg/dL).

The youngest daughter has been maintained under control of blood pressure and urinary infection episodes. Since then, she has been taking low doses of thiazides, magnesium hydroxide (400 mg/day) and vitamin D. Her renal function has been stable (serum creatinine = 0.9 mg/dL), nevertheless the ultrasound images of nephrocalcinosis has been progressively aggravated. Moreover, it has been observed the maintenance of mild hypomagnesaemia and hypercalciuria in this youngest girl. However, it seems that the drug and care interventions could be responsible for a reasonable control of serum ionic disturbance of Mg^{2+} and Ca^{2+} as well as uric acid and parathormone circulating levels achieving bone development and normal growth pattern. The results of the complementary tests from the two daughters and the father are summarized in Table 1. Figure 1 shows the index case radiologic aspects and retinopathy as well as the family heredrogram revealing affected ones and carriers. All subjects of this family gave us their consent to report any results.

Discussion

FHHNC is a disorder characterized by progressive renal Mg^{2+} and Ca^{2+} wasting and nephrocalcinosis leading to chronic renal failure. It could be considered that FHHNC was first described for Michelis *et al.* in 1972,[7] wherein familial magnesium wasting and acidosis was emphasized. Few years later, a more detailed description including the progressive nephrocalcinosis was done by Manz *et al.*, in 1978,[1] whereas the ocular involvement was more clearly highlighted by Meier *et al.*, in 1979.[2]

The key to understand those intriguing syndromes is based on the epithelial specialised function and relies on a group of substances known as claudins. Claudins are protein components of the tight junctions that work as a gate controlling the passage of ions and molecules across an epithelial barrier, regulating the cellular polarity, growth, and differentiation in fluid compartments of tissues such as kidney, inner ear and eyes.[4-6]

The differential diagnoses include a wide range of genetics tubular and metabolic disorders as well as macular lesions. The first point comes from the hypercalciuric syndromes group. They share an usual presentation of inherited disease, tendency to lithiasis, bone-mineral disturbance, electrolyte and acid-basic metabolism imbalance and growth retardation. Dent's disease has as hallmark hypercalciuria, low-molecular weight proteinuria and proximal tubular reabsorptive failure resembling the Fanconi syndrome, nephrolithiasis, nephrocalcinosis, renal function deterioration, and rickets. Because of its X-linked recessive trait, all daughters of an affected male are heterozygous and asymptomatic (but carriers), and 50% of sons from those female carriers will be affected. Hypomagnesaemia is almost always present in Gitelman's syndrome, but hypokalemic metabolic alkalosis, the hallmark of Bartter's and Gitelman's syndrome, is absent in FHHNC patients.[9-11]

A useful criteria used to make the diagnosis of FHHNC with ocular involvement has been hypomagnesaemia, urinary magnesium inadequately high to the blood level, hypercalciuria and nephrocalcinosis. The ocular involvement, with macular colobomata is a strong signal. Other very important points are: the onset in childhood, polyuria-polydipsia, recurrent urinary tract infections, nephrolithiasis, the progression to end stage renal disease in the teenager years associated with incomplete forms of tubular acidosis, hyperuricemia, and mildly elevated serum parathormone.[3,6] The pathogenesis of macular lesions is not well known, however a retinal development defect has been proposed.[5]

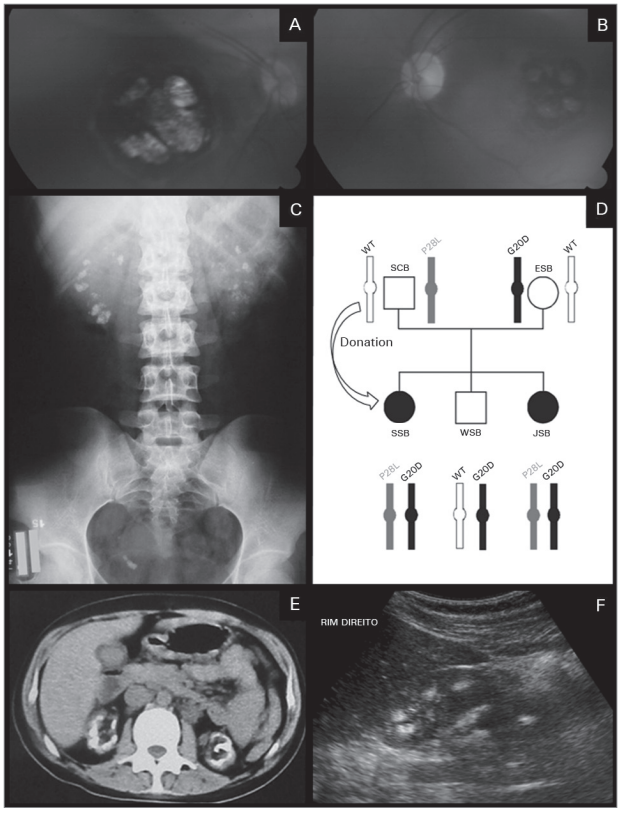
In some series the oral use of magnesium, vitamin D or citrate was not able to change the course of disease. Thiazides have also been used because the

Table 1 Blood and urinary tests before and five years after the transplantation

	SSB		SCB		JSB		
	before	after	before	after	before	after	Unit
Urea	320	33	31	34	27	37	mg/dL
Creatinine	12.6	1.2	0.9	0.7	1.1	0.9	mg/dL
Calcium	9.0	9.2	9.4	8.5	9.0	8.9	mg/dL
Magnesium	1.5	1.9	1.7	1.9	0.5	1.2	mg/dL
Phosphate	9.4	5.3	3.6	4.5	4.9	4.0	mg/dL
Total CO_2	20	24	28	25	24	22	mmol/L
Potassium	4.9	4.2	4.8	3.9	4.5	3.8	mmol/L
Chloride	104	102	105	106	107	106	mmol/L
Alkaline Phosphatase	139	43	62	54	137	78	U/L
Uric Acid	5.4	4.2	5.0	5.1	8.2	4.7	mg/dL
Total Proteins	7.4	6.4	7.2	7.6	8.5	7.3	g/dL
Albumin	4.7	4.1	4.5	4.7	5.2	4.4	g/dL
iPTH	468	16	32	43	80.3	36	pg/ml
Urinary Calcium	140	176	204	157	443	430	mg/24 horas
Urinary Magnesium	52	53	78	71	120	96	mg/24 horas
Urinary P/Cr Ratio	1087	456	102	125	840	640	mg/g

(SSB) are the initials to the kidney recipient, (SCB) to the donor and (JSB) to the youngest daughter.

Figure 1. Representative images from 19 years-old index case (SSB) before the transplantation and family heredrogram. (A) and (B) Left and right retinal images with bilateral colobomata. (C) Abdominal X-Ray film revealing calcifications images on renal shadows and right ureteral calculus. (D) The father to daughter donation and respective allelic mutations. SCB: the father donor; ESB: the mother; JSB: the youngest daughter; WSB: the son. (E) Abdominal computed tomography; and (F) Right kidney ultrasound scan revealing chronic contracted kidney and suggesting medullary nephrocalcinosis.



hypocalciuric effects, but the long term efficacy is not well established. Water intake and control of urinary infection recurrence are important.[3,4]

In conclusion, after five years of donation the renal graft function remained stable without recurrence of metabolic disturbances or nephrocalcinosis. Besides, donor single kidney Mg^{2+} and Ca^{2+} homeostasis associated to monoallelic status did not affect the safety and the usual living donor post-transplant clinical course.

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