FOUR CASES OF NEPHROPATHY IN CHILDREN WITH COENZYME Q10 DEFICIENCY INDUCED BY DIFFERENT GENE MUTATIONS AND LITERATURE REVIEW

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ABSTRACT

Objective*: To analyze the clinical characteristics, molecular biological characteristics and therapeutic effect of children with coenzyme Q (CoQ) nephropathy induced by different gene mutations, and review relevant literature.*

Methods: *The medical history, laboratory examination, treatment and prognosis of 4 cases clin-ically diagnosed with CoQ deficiency induced by different gene mutations admitted to the Department of Renal Rheumatology of our hospital from January 2017 to January 2020 were collected and analyzed, including 3 cases of CoQ8 mutation and 1 case of CoQ6 mutation.*

Results: *All of the 4 children with CoQ10 deficiency had a family history, and through renal biopsy, the pathology type was identified as FSGS, mostly associated with steroid resistance. Among them, homozygous mutation occurred at a young age and had obvious symptoms. While CoQ8 heterozygous mutation caused severe renal tubular lesions and early renal failure. All of the 4 mutations belonged to locus mutations.*

Conclusion: *Different gene mutations can lead to nephrotic syndrome, mostly manifested as steroid-resistant FSGS, but the clinical phenotypes and progression of CoQ deficiency induced by different gene mutations vary with symptoms. Early CoQ10 supplement therapy has a good curative effect on children with CoQ nephropathy, but in the event of severe renal injury, the progression of the disease should be controlled with conventional drugs, such as cyclosporine and tacrolimus.*

Keywords: *Gene mutation, CoQ, nephropathy, clinical characteristics, prognosis.*

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Introduction

Steroid-resistant nephrotic syndrome (SRNS) is one of the common types of kidney disease in children, which can progress to the end stage (end-stage renal disease, ESRD). Some children have such characteristics as young onset and poor hormone response, etc.[1]. In recent years, with the improvement and popularization of molecular diagnostic techniques, more and more studies have shown a close relation between SRNS-related genotypes and the clinical effect and prognosis of such children. This kind of nephropathy is also known as hereditary drug-resistant nephrotic syndrome[2]. At present, it is reported that the pathogenic variants of more than 60 single genes can lead to hereditary SRNS. Among them, the pathogenic variants of PDSS2, CoQ2, CoQ6 and CoQ8 genes can result in CoQ10 biosynthesis disorder and further induce renal lesions[3]. Such kind of nephropathy belongs to mitochondrial renal injury. Children with mitochondrial renal injury are often complicated by progressive encephalopathy, dystaxia, epileptic seizure, mental retardation, deafness, retinopathy, hypertrophic cardiomyopathy and systemic myopathy, etc[4].The author's team adopted next-generation sequencing on some children with primary nephrotic syndrome, who showed SRNS and had high genetic risk, and found 4 cases

of CoQ10 deficiency nephropathy induced by different gene mutations. The children varied in clinical characteristics and treatment. In the meantime, relevant literatures were reviewed. Below, the process will be reported.

Data and methods

Data of the cases

4 cases clinically diagnosed with CoQ deficiency induced by gene mutations admitted to the Department of Renal Rheumatology of our hospital from January 2017 to January 2020. All of them sought medical services due to the onset of nephrotic syndrome and were ster-oid-resistant, which were confirmed by renal biopsy and genetic testing. Their hearing and vision were normal, without obvious lag in growth and development.

Methods

All children were treated in our department, and their medical history, renal biopsy, laboratory examination, treatment and prognosis were collected. The gene mutation test was done by KingMed.

Results

General data

The 4 children were aged 4 years, 5 years, 3 years and 10 months, and de-noted as Examinees 1~4 respectively. Among them, the first two cases were brother and sister, Examinee 4 had a family member with nephrotic syndrome. The renal biopsy report indicated that all of them belonged to focal segmental glomerulosclerosis.

Among them, Examinee 1 progressed to ESRD and underwent renal transplantation, Examinee 2 was complicated by renal tubular injury, and Examinee 4 conformed to focal segmental glomerulosclerosis (cellular type) in renal biopsy and had now progressed to Stage II chronic kidney disease. All of the parents of 4 children de-nied consanguineous marriage. They were healthy in physical examination and showed no abnormality in urine test.

Characteristics of gene mutations

Among the 4 children with gene mutations, there were 2 cases of CoQ8 heterozygous mutation, 1 case of CoQ8 homozygous mutation and 1 case of CoQ6 heterozygous mutation. 2 cases of CoQ8 heterozygous mutation were brother and sister, i.e., Examinees 1 and 2.

The gene CoQ8B had heterozygous mutation where the base G>A at chr19:1211271, making the amino acid at position 150 mutate from arginine to glutamine, and had heterozygous mutation where the base G>C at chr19: 41209497, making the amino acid at position 250 mutate from aspartate to histidine. The brother and sister had the same clinical symptoms. There was 1 case of CoQ6 heterozygous mutation, i.e., Examinee 3, who had heterozygous mutation at c.A170T and c. T1298C.

There was 1 case of CoQ8B heterozygous mutation, i.e., Examinee 4, who had homozygous mutation at rs769834604 and the mutation originated from the genomes of his parents, i.e. both of his parents were heterozygous at this locus.

The parents had no clinical manifestations. The gene sequencing maps of Examinees 1/3 and their parents were shown in Figures 1-2.

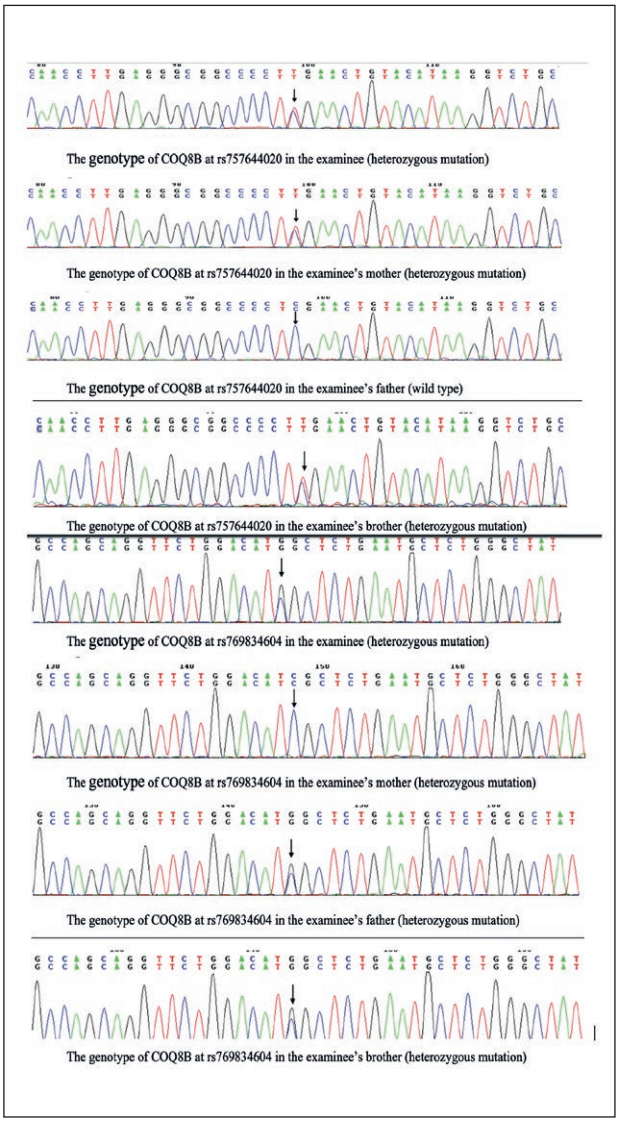

Figure 1: The gene sequencing maps of examinee 1 and his family.

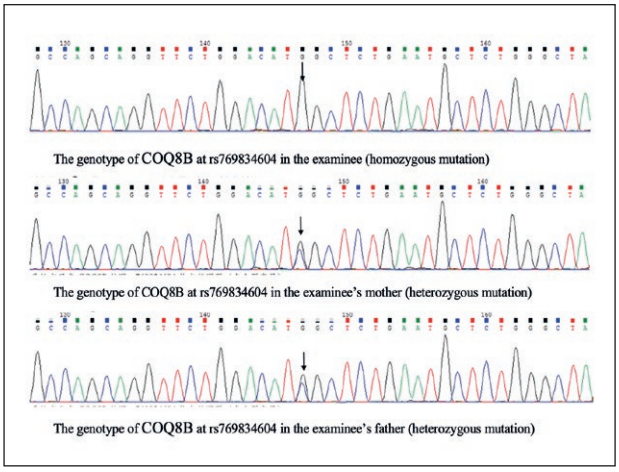

Figure 2: The gene sequencing maps of examinee 4 and his family.

The clinical data of Examinee 2 were shown in Tables. 1~2. Among them, Examinee 1 had no baseline treatment data for he underwent renal transplantation prior to genetic diagnosis.

The downward trend of the 24-hour urinary protein level of Examinees 2~4 three months before treatment was shown in Figures. 3~5.

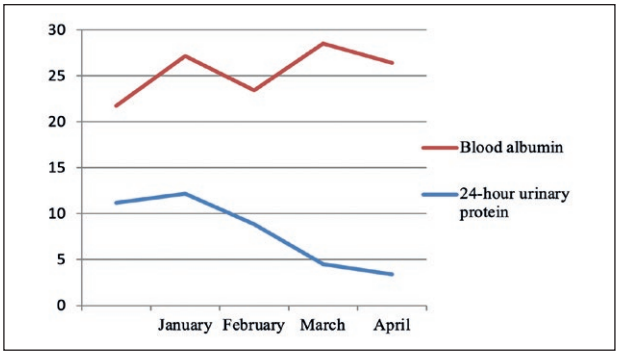

Figure 4: The downward trend of the 24-hour urinary protein level of examinees 3 three months before treatment.

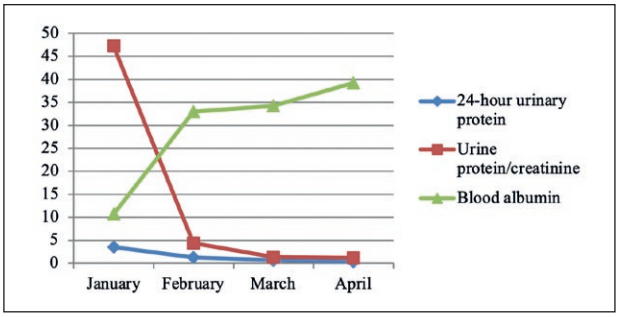

Figure 5: The downward trend of the 24-hour urinary protein level of examinees 4 three months before treatment.

Name	Age of Onset	Course of Disease	4-hour Urinary Protein at the Beginning of Disease	Urinalysis at the Beginning of Disease	Urine Protein/ Creatinine at the Beginning of Disease	Growth and Development	Blood Albumin	Serum Creatinine at the Beginning of Disease	Hearing and Vision Test
Examinee 2	5 years	6 years	4.25g/24h	Pro2+~3+ RBC2+~3+	2.72	No obvious lag	22g/l	27	Normal
Examinee 3	3 years	2 years	4.35g/24h	Pro3+ RBC1+	4.56	No obvious lag	32.9g/l	17	Normal
Examinee 4	10 months	2 months	6g/24h	Pro3+ RBC1+~2+	33.57	No obvious lag	15.42g/l	14	Normal

Table 1: Baseline clinical data of examinee 2.

Name	24-hour Urinary Protein	Urinalysis	Urine Protein/Creatinine	Blood Albumin	Serum Creatinine	Growth and Development	Other Systematic Injury
Examinee 2	0.44g/24h	Pro+ RBC-	1.78	39g/l	70	Normal	-
Examinee 3	4.16g/l	Pro3+ RBC1+	13.5	14.96g/l	31	Below P3	-
Examinee 4	0.63g/24h	Pro- RBC-	1.31	34.24g/l	26	Normal	-

Table 2: Clinical indicators of examinee 2 after 3 months of CoQ10 treatment.

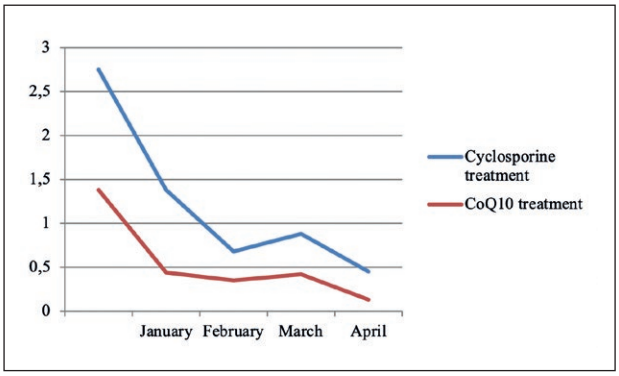

Figure 3: The downward trend of the 24-hour urinary protein level of examinees 2 three months before treatment.

Discussion

Steroid-resistant nephrotic syn-drome has poor prognosis and often progresses to ESRD. More than 20% of patients don't respond to hormone. These steroid-resistant children often progress to ESRD and need dialysis or renal transplantation[5]. While nephrotic syndrome induced by CoQ10 deficiency has a young onset, a long course of disease and severe pathological injury. Most of the children show steroid resistance or steroid dependence. Without adequate knowledge of this disease, it is extreme-

ly easy to neglect this disease and make it progress to ESRD[6]. Therefore, a key challenge in disease management is to identify children with poor steroid re-sponse and understand the potential pathogenesis of this disease. According to research, mutations in CoQ10 biosynthesis pathway can be found in 1% of SRNS children (in CoQ2, CoQ6, PDSS1, PDSS2 and CoQ8/ADCK4 genes)[7], so it is particular important to improve the understanding of such disease by clinicians under the concept of modern precision medicine. Since the CoQ6 gene mutation nec-essary for CoQ10 biosynthesis was first reported in steroid-resistant FSGS chil-dren in 2011, research on nephropathy induced by CoQ10 deficiency has become increasingly in-depth. It is found that SRNS/FSGS induced by human primary CoQ10 deficiency is related to four gene mutations (CoQ6, CoQ2, CoQ8, PDSS2) of them[8]. Meanwhile, CoQ10 nephropathy induced by different gene mutations has different clinical phenotypes, but with respect to treatment, high-dose CoQ10 can prevent or relieve the progression of renal disease in children with CoQ6, CoQ2 and CoQ8 mutations[9].

CoQ10 is an oil-soluble vitamin-like substance found in most eukaryotes (mainly mitochondria). As an integral part of the electron transport chain, it gets involved in the aerobic respiration of cell and produces energy in the form of ATP. About 95% of human energy is generated in the above way[10]. So organs with higher energy demand (e.g. heart, liver and kidney) often have higher CoQ10 concentration. Due to mitochondrial dysfunction in podocytes, mutations of three CoQ10 biosynthetic genes, CoQ6, CoQ2 and decaprenyl diphosphate synthase subunit 2 (PDSS2), are associated with SRNS[11]. In mice with PDSS2 mu-tation, the administration of CoQ10 can lower proteinuria and reduce interstitial nephritis. Foreign literature has shown that the supplement of CoQ10 can improve the overall response of patients with focal segmental glomerulosclerosis complicated by CoQ8 mutation[12]. It is currently known that at least the mutations of 26 single genes can lead to SRNS, including genes related to CoQ synthesis. Primary CoQ10 deficiency is the only mitochondrial disease induced by gene mutation that can be cured at present, so it is of great significance to identify SRNS related to CoQ10 deficiency in the early stage[13].

In clinical work, for children with persistent proteinuria of unknown origin or SRNS, it is necessary to consider the possibility of CoQ10-related gene mutation, especially for children with a relatively old age and a long course of disease, whose pathology type is FSGS. If a child is suspected of CoQ10-related gene defect, he can be diagnosed with the help of gene sequencing. As for serological examination, blood lactate level can be measured, but it should be noted that normal blood lactate level cannot exclude CoQ10 deficiency. CoQ10 content can be indirectly determined by the activity of NADH-cytochrome C reductase or directly determined by high performance liquid chromatography[14]. If biochemical analysis or clinical manifestations prompt CoQ10 deficiency, it is necessary to carry out comprehensive genetic testing related to CoQ10 synthesis, so next-generation sequencing or whole genome sequencing will be more effective testing methods. If CoQ10 has been found to be deficient clinically, but pathogenic changes remain unknown, fibroblasts can be considered for the measurement of CoQ10 in skin, in order to evaluate whether there exists a high risk[15].

In terms of treatment, primary CoQ10 deficiency is the only mitochondrial disease induced by gene mutation that can be cured at present. But existing studies show that the supplement of high-dose CoQ10 is not effective for all children, and some children are sensitive to immunosuppressive agents. For children with impaired renal function, the supplement of CoQ10 cannot avoid the progression of the disease[16]. Moreover, homozygous mutation induced by CoQ10 deficiency usually indicates poor prognosis. In this report, Examinee 4 belongs to homozygous mutation and progress is still observed even after CoQ10 supple-ment therapy, the 24-hour urinary protein doesn't drop significantly, and the renal function advances. So if homozygous mutation is found in clinical diagnosis and treatment, apart from routine CoQ therapy, the use of immunosuppressive agents should be continued and the deterioration of renal function in children should be guarded against.

Although polygenic diseases are more common than monogenic diseases, the research of monogenic diseases provides a valuable opportunity for understanding the potential molecular mechanism of a specific disease. The mechanism insights gained from children with monogenic diseases in rare forms can usually be applied to common diseases. In this study, 4 children with CoQ10 deficiency induced by gene mutation are included, but different gene mutation types will directly affect the clinical manifestations and prognosis of disease. So in the actual clinical diagnosis and treatment process, doctors should raise their understanding of this disease and

give different diagnosis and treatment interventions depending on different mutation types.

There are also some deficiencies in this study: only 4 cases were included, and part of the data was incomplete, and more cases need to be accumulated to further confirm the research results.

In summary, different gene mutations can lead to nephrotic syndrome, mostly manifested as steroid-resistant FSGS, but the clinical phenotypes and progression of CoQ deficiency induced by different gene mutations vary with symptoms. Early CoQ10 supplement therapy has a good curative effect on children with CoQ nephropathy, but in the event of severe renal injury, the progression of the disease should be controlled with conventional drugs, such as cyclosporine and tacrolimus.

References

1) Rotig A, Appelkvist EL, Geromel V, et al. Quinone-responsive mul-tiple respiratory chain dysfunction due towide spread CoQ10 defi-ciency. Lancet, 2000, 356(9227): 391-395.
2) Diomedi-Camassei F, Di Giandomenico S, Santorelli FM, et al. CoQ2 nephropathy: a newly described inherited mitochondriopathy with primary renal involvement. J Am Soc Nephrol, 2007, 18(10): 2773-2780.
3) Heeringa SF, Chernin G, Chaki M, et al. CoQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. J Clin Invest, 2011, 121(5): 2013-2024.
4) Zhu JY, Fu Y, Richman A, et al. A Personalized Model of CoQ2 Nephropathy Rescued by the Wild-Type CoQ2 Allele or Dietary CoQ10 Supplementation. J Am Soc Nephrol, 2017, 28(9): 2607-2617.
5) Cao Q, Li GM, Xu H, et al. CoQ(10) treatment for one child with CoQ6 gene mutation induced nephrotic syndrome and literature review. Zhonghua Er Ke Za Zhi, 2017, 55(2): 135-138.
6) Gigante M, Diella S, Santangelo L, et al. Further phenotypic heterogeneity of CoQ10 deficiency associated with steroid resistant nephrotic syndrome and novel CoQ2 and CoQ6 variants. Clin Genet, 2017, 92(2): 224-226.
7) Brown EJ, Pollak MR, Barua M. Genetic testing for nephrotic syndrome and FSGS in the era of next-generation sequencing. Kidney Int, 2014, 85(5): 1030-1038.
8) Kirby DM, Thorburn DR, Turnbull DM, et al. Biochemical assays of respiratory chain complex activity. Methods Cell Boil, 2007, 80(4): 93-119.
9) Vasta V, Merritt JL 2nd, Sanetorp B, et al. Next-generation sequencing for mitochondrial diseases: a wide diagnostic spectrum . Pediatrics Int, 2012, 54(5): 585-601.
10) Giugliani R, Federhen A, Rojas MV. Mucopolysaccharidosis I, II, and VI: brief review and guidelines for treatment. Genet Mol Biol, 2010, 33(4): 589-604.
11) Al-Sannaa NA, Al-Abdulwahed HY, Al-Majed SI, et al. The clinical and genetic Spectrum of Maroteaux-Lamy syndrome (Mucopolysa cchaidosis VI) in the Eastern Province of Saudi Arabia. J Community Genet, 2018, 9(1): 65-70.
12) Desbats MA, Morbidoni V, Silic-Benussi M, et al. The CoQ2 genotype predicts the severity of coenzymeQ10 deficiency . Hum Mol Genet, 2016, 25(19): 4256–65.
13) Stańczyk M, Bałasz-Chmielewska I, Lipska-Ziętkiewicz B, et al. CoQ10-related sustained remission of proteinuria in a child with CoQ6 glomerulopathy-a case report . Pediatr Nephrol, 2018, 33(12): 2383-2387.
14) Yuruk Yildirim Z, Toksoy G, Uyguner O, et al. Primary CoQ10 Deficiency-6 (CoQ10D6): Two siblings with variable expressivity of the renal phenotype. Eur J Med Genet, 2020, 63(1): 103621.
15) Li GM, Cao Q, Shen Q, et al. Gene mutation analysis in 12 Chinese children with congenital nephrotic syndrome. BMC Nephrol, 2018, 19(1): 382-390.
16) Widmeier E, Airik M, Hugo H, et al. Treatment with 2,4-Dihydroxybenzoic Acid Pre-vents FSGS Progression and Renal Fibrosis in Podocyte-Specific CoQ6 Knockout Mice. J Am Soc Nephrol, 2019, 30(3): 393-405.

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