

Proteinuria in Frasier Syndrome

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SUMMARY

Introduction Frasier syndrome (FS) is a genetic form of glomerulopathy, which results from mutations in the Wilms' tumour suppressor gene (*WT1*). Proteinuria in FS has been traditionally considered unresponsive to any medication and FS inevitably progresses to end stage renal failure.

Case Outline We present a patient with FS who had atypical clinical manifestation and unusual beneficial antiproteinuric response to renin-angiotensin system (RAS) inhibitors given in combination with indomethacin. After 13 years of follow-up, the patient is now 17-year old with normal renal functions and no proteinuria.

Conclusion RAS inhibitors combined with indomethacin showed beneficial effect in our patient. Thus, this combination might be the initial treatment of patients with FS. If this treatment strategy was not satisfied for at least 3 months, then CsA would be considered to be administered taking account of the nephrotoxicity and the increased risk of malignancy. Further prospective study is required to clarify this issue.

Keywords: steroid resistant nephrotic syndrome; Wilms' tumour suppressor gene (*WT1*); angiotensin converting enzyme (ACE) inhibitor; angiotensin receptor blocker; indomethacin

INTRODUCTION

Frasier syndrome (FS) is a clinical entity consisting of progressive glomerulopathy with proteinuria that begins in childhood and progresses to end stage renal failure (ESRF) usually during the second decade of life. It was first reported in 1964 by Frasier et al. [1] in monozygotic twins with gonadoblastoma and pure gonadal dysgenesis. The presence of Wilms tumour (*WT1*) gene mutations in FS was described and characterized in 1997 by Barbaux et al. [2]. Heterozygous mutations in intron 9 of *WT1* result in deficiency of the lysine, threonine, and serine (KTS)-positive isoforms. The reversion of the normal KTS positive to negative ratio from 2:1 to 1:2 disturbs a precise balance between *WT1* isoforms, which is essential for normal function of *WT1* in gonadal and renal development [2, 3, 4].

FS is usually presented as a female phenotype with the absent pubertal development, a male karyotype (46, XY) and gonadal dysgenesis (streak gonads) predisposing to gonadoblastoma [5]. Female (46, XX) patients with normal female genitalia may also have FS due to *WT1* mutations [6-8]. Extremely rare, Frasier mutations may be observed in 46, XY phenotypic males [9].

The most common manifestation of the renal disease in FS is steroid resistant nephrotic syndrome (SRNS) associated with the histologi-

cal lesions of focal segmental glomerulosclerosis (FSGS) that slow progress to ESRF [10]. In addition, rare variants without typical histology lesions have been described [11, 12]. Nevertheless, ESRF can occur without the signs of nephrotic syndrome, even during early infancy [13, 14].

Despite many recent advances in the genetics and pathophysiology of FS [12, 14, 15], an appropriate clinical management of FS is still lacking. To date, there has been no effective treatment for this condition, and therapies to reduce proteinuria pose a major challenge for nephrologists.

We report on a long-term successful treatment of proteinuria with combination of renin-angiotensin system (RAS) inhibitors and non-steroidal anti-inflammatory drug (NSAID) in patient with FS who had unusual clinical presentation.

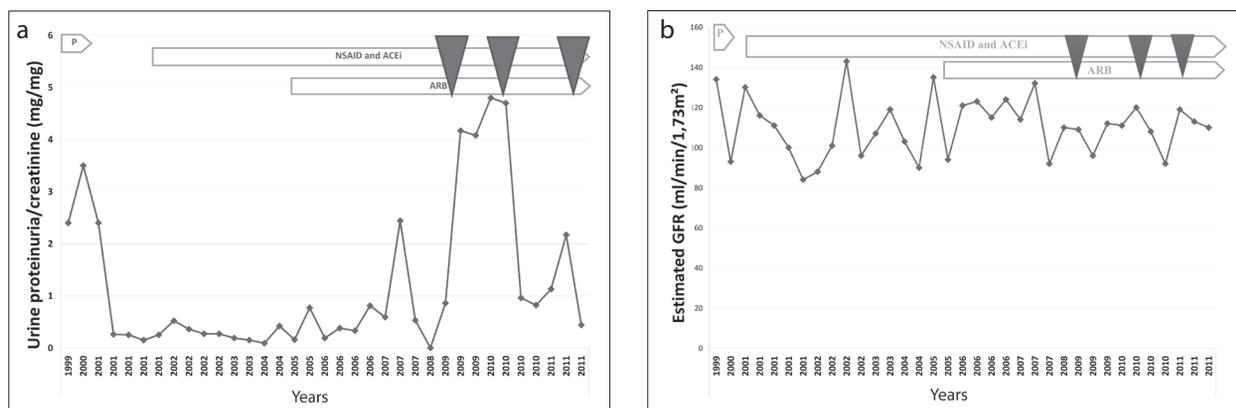
CASE REPORT

A four-year old girl was found to have isolated nephrotic range proteinuria during routine laboratory examination. She was the third daughter of non-consanguineous parents. The father received treatment for sarcoidosis.

Clinical examination was normal except for the skin and gingival hyperpigmentation. Sero-

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Graph 1. Trends of urinary protein/creatinine (a) and renal function (b) over time

Triangles indicate treatment discontinuation.

P – steroid therapy; ACEi – angiotensin-converting enzyme inhibitor therapy; NSAID – non-steroid antiinflammatory drug therapy (indomethacine); ARB – angiotensin II receptor blocker therapy

logic evaluation for syphilis, toxoplasmosis, rubella, hepatitis B, hepatitis C, varicella zoster, Epstein-Barr virus, Cytomegalovirus, Coxsackie, ECHO viruses, Borellia, Adenoviruses, Herpes simplex, Influenza A, B and Para- influenza, measles and human immunodeficiency virus were negative. Complement C3 and C4 were within normal limits. Antinuclear antibody, antibody to native DNA, anti-neutrophil cytoplasmic antibody, anti-mitochondrial and anti-Smith (Smith) antibodies were negative. Renal ultrasonographic examination did not reveal any structural abnormalities.

Endocrine investigations including baseline and ACTH-stimulated cortisol values were normal. On echocardiography, moderate pericardial effusion was discovered and later proved to be resistant to therapy. Kidney biopsy revealed mesangial proliferative glomerulonephritis with moderate activity. She failed to respond to prednisone at a dose of 60 mg/m²/day, so, after 8 weeks of treatment, we decided to taper the steroid therapy gradually until it was discontinued. In the follow up, no further immunosuppressive drug was given, and, instead, captopril, an angiotensin converting enzyme inhibitor (ACEI), and indomethacin, a non-steroidal anti-inflammatory drug (NSAID) were introduced to control the proteinuria. The dosage of each drug was increased gradually from 1 to 3 mg/kg/day. Proteinuria decreased to normal values, while glomerular filtration rate remained normal (Graph 1a). The second kidney biopsy was performed 3 years after the first biopsy. Mesangial proliferative glomerulonephritis was confirmed.

In the following years, the patient had normal growth and development but pericardial exudation gradually increased. At her age of 10 years, the cardiologist prescribed colchicine (0.25 mg/day) while indomethacin and captopril were temporarily discontinued. The treatment with colchicine was unsuccessful in terms of reducing the pericardial effusion. Pericardiocentesis was performed due to life threatening cardiac tamponade. Serous exudate in volume of 260 ml was evacuated without relapse during the further follow-up. The comprehensive exudate analyses (cytological, biochemical, bacteriological and immunological) yielded negative findings. The treatment with captopril and indomethacin was reintroduced with the ad-

dition of angiotensin receptor blocker (ARB), valsartan. Later on, captopril was replaced by enalapril and valsartan by losartan.

At the age of 15 years, delayed puberty was diagnosed (puberty stage Tanner B1, P1 and primary amenorrhea). Ultrasonographic examination showed infantile uterus but ovaries were absent. Chromosomal analysis showed a male karyotype (46 XY). Direct sequencing of *WT1* uncovered a heterozygous donor-splice site mutation (i.e. IVS9+5G>A). Exploratory laparotomy was performed and revealed bilateral streak gonads which were removed to preclude the risk of gonadoblastoma. The histology showed no evidence of malignancy.

At the last check-up, the patient was 17 years old with body height of 175 cm, body weight of 53 kg and with blood pressure 100/60 mm Hg. The patient's glomerular filtration rate was normal (serum creatinine of 75 µmol/l) with no apparent proteinuria (< 200 mg/day). Echocardiographic finding was normal. As of now, the patient is receiving enalapril (20 mg/day), losartan (50 mg/day), indomethacin (75 mg/day) and an appropriate hormone substitution (Cyclo-progynova).

During 13 years of follow-up, the antiproteinuric therapy (ACEI/ARB/indomethacine) was discontinued on several occasions (Graph 1b). Temporary interruptions of the drugs were associated with relapses of proteinuria. After re-administration of the drugs, favourable responses were achieved again.

DISCUSSION

Prevalence of FS is not known. Most of the reported patients are individual cases or small case series [1, 6-14, 15, 16-21]. Genetic analyses in patients with SRNS have revealed that FS is not as rare as previously thought. Prevalence of *WT1* splice mutations (i.e. IVS9+5G>A and IVS9+4C>T) in FS has been reported as 9.35% in the group of 32 children with SRNS [12].

Our patient had atypical clinical presentation and unusual beneficial antiproteinuric response to RAS inhibitors

given in combination with NSAID. An association between FS and chronic pericardial effusion was also described in another patient with FS [22] but this association has remained unexplained. A gingival hyperpigmentation found in our patient has not been reported previously. This might be an unusual presentation of FS or may simply be a coincidental. The suspicion of underlined systemic disease led to delayed diagnosis of FS in our patient. Nowadays, it is suggested to do genetic analysis in all patients as soon as steroid resistance is confirmed to avoid unnecessary immunosuppressive therapy [20].

It has been recognized before that severe proteinuria itself is a renal toxin; if left untreated, the patients would invariably have an inexorable progression to ESRF [23, 24, 25]. The traditional assumption that proteinuria is unresponsive to any medications in genetic forms of SRNS has been questioned recently [26]. Treatment with calcineurin inhibitors was found to induce remission of proteinuria in several children with the genetic forms of SRNS [27, 28, 29] by stabilizing the actin cytoskeleton in the podocytes [26, 29, 30]. Nevertheless, therapy with calcineurin inhibitors in patients carrying *WT1* mutations may be complicated by nephrotoxicity and the increased risk of malignancy. Renin-angiotensin system (RAS) blockade via angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin-receptor blockers (ARB) is an alternative treatment to protect the remaining glomeruli from hypertrophy, intraglomerular hypertension, and progressive sclerosis, not only by lowering blood pressure but also by their antiproteinuric, antifibrotic, and anti-inflammatory properties [31]. A further reduction in urinary proteins was found when other antiproteinuric drugs, such as NSAIDs, mostly indomethacin [32, 33, 34], were given in combination with conventional RAS antagonists. Combination of post-glomerular vasodilatation by ACEI and pre-glomerular vasoconstriction by indomethacin results in reduction of the transcapillary hydraulic pressure and decrease of the capillary wall permeability. This combination has already been success-

fully used in patients with the genetic glomerulopathy such as congenital nephrotic syndrome of the Finnish type [35] and in patients with the diffuse mesangial sclerosis [36]. To the best of our knowledge, this is the first report of FS that achieved complete remission in term of proteinuria, while the patient was only on renoprotective measures including the use of RAS inhibitors and NSAID.

In view of the consistent association of antiproteinuric efficacy with long-term renal outcome and high risk for malignancy in FS, we propose ACEI and indomethacin as the first line therapy in patients with FS. If necessary, the antiproteinuric efficacy could be enhanced by adding ARB. Such strategy would require that titration for adequate blood pressure control is followed by titration for a maximal antiproteinuric effect without increasing the side effects (i.e. reduced GFR, hyperkalemia and drug toxicity). If this treatment strategy was not satisfied for at least 3 months, then CsA would be considered to be administered taking account of the nephrotoxicity and the increased risk of malignancy [29].

In conclusion, our observation of a case presenting with an early nephrotic proteinuria associated with the skin and gingival hyperpigmentation and exudative pericarditis may expand the clinical spectrum of Frasier syndrome. ACEI/ARB and NSAID showed beneficial effect and may be appropriate therapeutic options in FS patients. If this treatment strategy was not satisfied for at least 3 months, then CsA would be considered to be administered taking account of the nephrotoxicity and the increased risk of malignancy. Further prospective study is required to clarify this issue.

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Протеинурија у Фразијеовом синдрому

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КРАТАК САДРЖАЈ

Увод Фразијеов (*Frasier*) синдром (ФС) је наследна гломерулопатија која настаје као последица мутације супресорног гена Вилмсовог (*Wilms*) тумора (*WT1*). Традиционално је схватање да се протеинурија у ФС не може лечити и да се ова болест неминовно завршава терминалном слабошћу бубрега.

Приказ болесника Представљамо болесника са ФС који је имао нетипичну клиничку слику и необично добар одговор на лечење инхибиторима ренин-ангиотензин система (РАС) и индометацином. После 13 година лечења седамнаестогодишњи болесник има нормалну општу функцију бубрега и нормалну протеинурију.

Закључак Инхибитори РАС у комбинацији с индометацином показали су повољно дејство на исход лечења приказаног болесника са ФС. Можда би ова комбинација лекова могла бити избор почетне терапије за ове болеснике. Ако ова терапија нема повољан ефекат у року од најмање три месеца, онда долази у обзир циклоспорин, с тим да се мора водити рачуна о његовом нефротоксичном и онкогеном дејству. Потребна су даља проспективна истраживања да би се утврдио терапијски протокол за ФС.

Кључне речи: стероид-резистентни нефротски синдром; супресорни ген 1 Вилмсовог тумора (*WT1*); инхибитор ангиотензин-конвертујућег ензима (*ACE*); блокатор рецептора ангиотензина; индометацин