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RARE DISEASES WITH RENAL INVOLVEMENT IN THE REPUBLIC OF MACEDONIA

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A b s t r a c t: Rare diseases (RDs) pose a significant set of problems for patients, since their disease and general social and health situation are often not recognized by the medical community and shunned by health insurance. The sheer number of RDs (5000–8000) and the number of patients (6–8% of the population) are challenging for every society. We wanted to get a better understanding of the rare diseases affecting the kidneys and urinary tract (RDAKUT) in the Republic of Macedonia and we investigated principally the PubMed Central articles of Macedonian medical professionals dealing with RDAKUT, but we also used information on RDAKUT from local sources. A significant number of RDs have been published, demonstrating the awareness and skill of Macedonian medical professionals despite pretty limited diagnostic facilities. We still feel that RDAKUT are under-diagnosed (e.g. Fabry's disease has not yet been reported), and that many patients with RDs have a long way to go before an accurate diagnosis. Increased awareness and ameliorated education are needed by the physicians; while health insurance must include RDAKUT covering their diagnosis and treatment costs. Neonatal screening for ~30 diseases (instead of just hypothyroidism) is also required. Patients' organizations exist and they are active in promoting their interests before of the health authorities.

Key words: rare diseases, Macedonia, kidneys, urinary tract, genetics.

Introduction

A rare disease (RD) is one which affects less than one citizen in 2000 (Europe), and less than one in 1250 (USA). The general estimation is that there

are 6000–8000 RDs, and their number is growing [1]. About two thirds of RDs affect children, and a third of them die before their fifth birthday. RDs weigh heavily on the health systems of every country: there are at least 3 million patients with RDs in the UK, 4 million in Germany, and as many as 30 million EU citizens [1]. Thus the patients, their families, health insurers and societies as a whole are impacted with a set of great organisational, financial, diagnostic and treatment challenges.

What is the situation with RDs in the Republic of Macedonia, particularly those affecting kidneys and the urinary tract (RDAKUT)? First, no official registries exist at the national level. Therefore the full picture and the consequences for our society are not known. We looked through the PubMed central and other local data sources in order to get some insight into the RDAKUT in Macedonia.

Methods

Since Macedonia is a small country (2 million inhabitants) the whole scientific and clinical work with patients suffering from RDAKUT is concentrated at the University Clinics and Institutes at the Medical School, Skopje. The research strategy targeted clinicians and scientists working at the University Children's Hospital, Skopje, the Nephrology Clinic, the Urology Clinic, the Department of Radiology, the Department of Nuclear Medicine, the Institute of Pathology, the Institute of Immunology and the Research Centre for Genetic Engeneering and Biotechnology at the Macedonian Academy of Sciences and Arts. Firstly, a search through the PubMed central was performed using the term Macedonia/Macedonian in combination with one or more of the following terms such as: rare diseases, kidney, renal, genetic, glomerulonephritis, nephrotic, proteiuria, hypertension, nephrolithiasis, urolithiasis, haematuria, cystic, polycystic, dysplasia/dysplastic, congenital anomalies, urinary tract, acidosis, glucosuria, tubular, chronic kidney diseases, chronic renal failure. Over 150 clinicians and scientists from the above-mentioned Institutions were checked to see if they had a publication cited in PubMed. The other source was the Bulletin of the Medical Faculty Skopje, containing abstracts from Conferences and Congresses. For details authors were contacted and requested to supply appropriate information.

Results

Under the term Macedonia and Macedonian we found 1347 and 229 citations respectively in PubMed. We narrowed the numbers for analysis, adding

a key word: haematuria, n = 8; proteinuria n = 25; kidney n = 121; renal n = 135, hypertension 48, chronic renal failure 57; chronic kidney diseases 71, glomerulonephritis n = –32; nephrotic n = 16; nephrolithiasis n = 5; urolithiasis n = 4; cystic n = 25; polycystic n = 5; dysplasia n = 4; dysplastic n = 1; congenital anomalies n = 25; urinary tract n = 45; acidosis n = 4; glucosuria n = 1; tubular n = 11. All these publications were reviewed further in order to identify rare disorders and to characterize them as: a) primary renal disorder b) systemic or metabolic disorder with secondary affection of the kidneys c) syndromatic disorder with renal component. Also the ethnicity of the patients was analysed, and included only those who were born or lived in Macedonia. RDAKUT affecting Macedonians are reported in Table 1 [2–39]. It is evident that the majority of published RDAKUT are genetic in nature, primarily tubulopathies, and reported from a pediatric institution as single case reports (Barter syndrome, FHHNC, Lesch Nyhan syndrome, renal coloboma syndrome [2, 5, 14, 20] or within collaborative multicentric studies (Dent disease, Lowe syndrome, renal tubular acidosis, renal glucosuria, etc [6, 9, 10, 11, 13, 17]. On the other hand the reports from adult nephrologists mainly deal with glomerulonephritis, systemic vasculitis and amyloidosis [31, 32, 34, 35, 37, 39–42]. Although Balkan nephropathy is endemic in areas outside Macedonia, there are several reports in which Macedonian nephrologists make a significant contribution due to their accumulated experience in diagnosis and management of this rare/endemic disease [25–30]. Some of the reports deal with a combination of two rare diseases, as in the case of renal tubular acidosis and hereditary renal hypouricaemia, nephrotic syndrome and thyroid disease, etc. [43–45]. It is interesting that rare diseases with autosomal recessive inheritance such as cystinuria, FHHNC and ARPKD have been observed in two generations. We could not identify any patient with cystinosis, Fabry disease or nephronophtisis. Macedonian physicians also reported metabolic diseases which certainly affect kidneys such as primary hyperoxaluria, which was diagnosed for the first time in a graft biopsy with the presence of calcium oxalate crystals and subsequently confirmed with mutational analysis of the AGXT gene [15]. Secondary Fanconi syndrome was evidenced in patients with galactosaemia and thyrosinemia and nephrolithiasis in a patient with glucose galactose malabsorption [23]. Adult nephrologists reported cases of familial nephrotic syndrome. In contrast, paediatric nephrologists routinely checked all children with corticoresistant nephrotic syndrome for mutations in the NPHS2 and WT1 gene, but up to now only one heterozygous carrier of NPHS2 mutation has been detected (unpublished data). A patient with congenital nephrotic syndrome was diagnosed clinically as having Denys Drash syndrome and a novel mutation in the WT1 gene detected (unpublished data). Concerning the age of diagnosis of RDAKUT we could not obtain accurate data; although a few patients were diagnosed in the neonatal period due to the severity of clinical and renal manifestation, as in the case of distal renal tubular

acidosis. On the other hand there were patients whose diagnosis was established late in adulthood or post-transplant due to a mild and atypical clinical course (primary hyperoxaluria), lack of diagnostic facilities (electronomicroscopy for Alport disease, or simple nitroprusside test for cystinuria).

Discussion

Rare disease with kidney affection pose significant problems to health care providers. In the majority of cases multiple systems and organs are affected requiring specialized care by different medical specialists [46]. Ultimately, many of these diseases terminate in uraemia. Such for example is a Bardet Biedl syndrome, a multisystem disorder characterized with obesity, polidactyly, mental retardation, retinal dysplasia, hypogonadism, congenital heart defect and renal affection. Multidisciplinary treatment includes surgery for heart defect and polydactyly, and regular neurological, endocrinological, ophtalmological and developmental check-ups with special rehabilitation. Nowadays renal affection is recognised as a major component of the disease, and in many cases these patients approach terminal renal failure most often due to renal dysplasia [47]. It is a similar situation with VACTERL association in which a good quality of life may be achieved with multiple surgeries [48]. We have seen such a patient who was born with a tracheoesophageal fistula, anal atresia, ventricular septal defect and a multicystic kidney. The baby underwent successful emergency surgery in the neonatal period, the ventricular septal defect closed spontaneously and the same happened with muylticystic kidney (spontaneous resolution of the cysts). The family agreed to participate in the project for the detection of candidate genes for CAKUT and pathogenic mutation was found in the HNF1B gene [18]. Although this is primarily a scientific project there are two obvious benefits for the family, the index case will have regular check-ups for early detection of diabetes (in this case a high risk of the development of MODY 5 diabetes) and implementation of preventive measures. The second benefit is that this family will have the chance of proper genetic counselling and screening will be offered to other family members. The index patient will have chance of accurate prenatal diagnosis. In his review of genetic renal diseases in T*he Lancet* Hildebrandt has recently summarized the advances of molecular techniques which enable the establishment of molecular diagnosis for many diseases, even in individual patients [49]. Therefore many researchers and clinicians use the term ‘personalized medicine’ [49, 50]. This opens many ethical dilemmas particularly in those patients in whose genome variants of unknown significance are detected.

These newly discovered genes, proteins, and pathways can represent powerful new drug targets. Therefore it is of ultimate need to understand the

pathophysiology of many rare diseases. In that respect it is crucial to intensify clinical, genetic, and pathophysiological research on rare diseases but also to increase the awareness of the community and health authorities of the problem of rare diseases on the local and national as well international levels [51–54]. One should expect that with advances in research, sequencing of the human genome, and development of high-throughput genomic and post-genomic tools, mechanisms of many rare genetic disorders affecting the kidneys will be clarified in the coming years. There is great promise that innovative biotechnological research including monoclonal antibodies, enzyme replacement therapy, cell and gene therapy, as well as classical therapeutic research based on the search for active chemical compounds will significantly improve the treatment of patients with RDAKUT [51, 53]. We have diagnosed two rare genetic diseases (hereditary renal hypouricaemia and renal glucosuria) and confirmed the diagnosis with mutational analysis of the respective genes. Both the diseases are the result of defective transporters for glucose and urate on the luminal membrane of the tubular cell. Better knowledge of these transporters, their structure and function can lead to the discovery of new drugs with the potential to inhibit these transporters and result in uricosuric and glucosuric effect and, finally, will widen our armamentarium for the treatment of gouty hyperuricaemia and *diabetes mellitus*.

What is the situation with RDAKUT in Macedonia? It seems that Macedonian nephrologists and paediatricians have limited experience in the diagnosing and treatment of the "most popular" rare disease described in textbooks. For example, two children with Lowe syndrome were diagnosed very late (at the age of 1.5 and 12 years) [12]. Is this the result of lack of knowledge or of proper screening tests? The hallmark of Lowe syndrome is congenital cataracts and if screening was available in the neonatal period these patients would not escape the proper diagnosis. In contrast, we have implemented screening for tubular proteinuria in children referred to the paediatric nephrology clinic by using the relatively old method SDS-PAG electrophoresis of urinary proteins and have diagnosed many tubular disorders, among them three patients with Dent-2 diseases [a total of 28 patients according to Bokenkamp *et al*. [9]].

What about metabolic diseases with kidney affection? Without comprehensive and good metabolic screening there is no prevention of renal lesion which may eventually lead to renal failure. There is no neonatal screening for primary hyperoxaluria, but paediatric and adult nephrologists should measure oxalate in all patients with recurrent or bilateral nephrolithiasis. Spasovski *et al*. reported a 50-year-old female patient who was diagnosed with primary hyperoxaluria type 1 due to early graft failure [15]. Interestingly, this patient had only one episode of passage of calculus and did not alert the clinicians to the possibility of such a disastrous metabolic disease. Although the compound heterozygous mutations found in this patient have already been reported and manifested with early and severe disease, the influence of other genetic and environ-

mental factors on the relatively mild pretransplant disease course in our patient cannot be excluded.

As we have mentioned in the "results", there were no reports on cystinosis, nephronophtisis and Fabry disease. It seems that cystinosis is an extremely rare diseases in Macedonia; and in the florid form could not escape diagnosis at the late stage with development of multiorgan dysfunction, particularly typical ocular changes and Fanconi syndrome. Nephronophitis could be overlooked, particularly if a biopsy was not performed. We believe that Fabry disease is underdiagnosed in R. Macedonia due to lack of knowledge and familiarity with this disease. It is of utmost interest to search for this disease in chronic renal failure patients using a specially designed questionnaire. Slovenia is also a small country, but the first patient with Fabry disease was diagnosed in 1991 and since then many cases of that disease have been diagnosed, familial screening implemented and enzyme replacement treatment commenced [55, 56].

In conclusion, this is the first work aimed at identifying clinicians and researchers from Macedonia working with RDAKUT. Although this study faced problems in collecting information on this topic, we believe that establishing a national network on rare diseases and particularly a registry on RDAKUT will give a great input to early and accurate diagnosis of these diseases and enable access to the best treatment modalities for these patients.

Table 1

Rare disease with renal involvement in the Republic of Macedonia

Rare Disease (number of patients)	Characterisation of the disease	Renal affection	Diagnosis confirmed	Reported
Antenatal Barter Syndrome (3)	Primary renal	Tubulopathy, nephrocalcinosis	Biochemistry, DNA study	PubMed (2)
FHHNC (4)	Primary renal	Tubulopathy, nephrocalcinosis	Biochemistry, DNA study	PubMed (3, 4, 5)
Distal renal Tubular acidosis (12)	Primary renal	Tubulopathy, nephrocalcinosis	Biochemistry, DNA study	PubMed (6, 7)
Cystinuria (15)	Primary renal	Nephrolithiasis	Biochemistry, DNA study	PubMed (8)
Dent-2 disease (3)	Primary renal	Proximal tubulopathy	Biochemistry, DNA study	PubMed (9, 10, 11, 12)
Lowe syndrome (2)	Systemic disease	Proximal tubulopathy	Biochemistry, DNA study	PubMed (12, 13)
Hereditary renal hypouricemia (9)	Primary renal	Kidney stones	Biochemistry, DNA study	Abstract
Lesch-Nyhan disease (1)	Metabolic	Stones, Urate nephropathy	Biochemistry, DNA study	PubMed (14)

Primary Hyperoxaluria type 1 (5)	Metabolic	Stones, nephrocalcinosis	Biochemistry, DNA study	PubMed (15, 16)
Renal glucosuria (6)	Primary renal	Glucosuria	Biochemistry, DNA study	PubMed (17)
ARPKD (7)	Renal/Liver	Nephromegaly, cysts, CRF	Biochemistry, DNA study	Abstract
Renal cysts/Diabetes syndrome (2)	Systemic	Renal dysplasia, VUR	DNA study	PubMed (18)
BOR syndrome (1)	Syndromatic	VUR, dysplasia	DNA study	PubMed (18)
Bardet Biedl syndrome (3)	Syndromatic	Renal dysplasia, CRF	DNA study	abstract
Town-Brocks syndrome (1)	Syndromatic	VUR, duplex system	DNA study	unreported
Alport syndrome (9)	Syndromatic	Haematuria, proteinuria, CRF	DNA study	PubMed (19)
Thin membrane disease (4)	Primary Renal	Haematuria	DNA study	unreported
Renal Coloboma syndrome (1)	Syndromatic	Multicystic kidneys	DNA study	PubMed (20)
VACTERL (6)	Syndromatic	Multicystic kidneys, VUR	Imaging studies	abstract
Pradder Willy Syndrome (1)	Syndromatic	VUR, reflux nephropathy	FISH	unreported
Pseudoxanthoma elasticum (5)	Multisystem	Hypertension	DNA study	PubMed (21)
Thyrosinemia (2)	Metabolic	Renal Fanconi syndrome	Biochemical	unreported
Galactosemia (2)	Metabolic	Renal Fanconi syndrome	Biochemical, DNA study	unreported
Alstrom syndrome (2)	Syndromatic	Renal dysplasia	Biochemical, DNA study	PubMed (22)
Glucose galactose malabsorption (2)	Metabolic	Nephrolithiasis	Biochemical, DNA study	PubMed (23)
Idiopathic infantile hypercalcemia (3)	Metabolic	Nephrocalcinosis	Biochemical	Abstract
Sarcoidosis (1)	Systemic	Nephrocalcinosis	Biochemical	Abstract
Pheochromocytoma (1)	Neoplastic	Renal artery stenosis	Biochemical, imaging	PubMed (24)
Balkan nephropathy (NA)	Primary renal	Tubulopathy, CRF	Biopsy	PubMed (25–30)
Corticoresistant nephrotic syndrome (14)	Primary renal	Nephrotic syndrome, CRF	Biopsy	PubMed (31, 32)
Denys Drash syndrome (1)	Syndromatic	Nephrotic syndrome, CRF	DNA study	unreported
Burkitt lymphoma (1)	Neoplastic	Billateral cystic kidneys	Tumour biopsy	PubMed (33)

Lipoprotein glomerulopathy (2)	Primary renal	Proteinuria, CRF	Biopsy	PubMed (34)
Essential monoclonal cryoglobulinaemia (1)	Neoplastic	Glomerulonephritis	Biopsy	PubMed (35)
Kawasaki Disease (1)	Systemic	Sterile pyuria/TIN	Clinical	PubMed (36)
Takayasu arteritis (1)	Vasculitis	Renovascular hypertension	Imaging	PubMed (37)
Donohue syndrome (1)	Syndrtomatic	Nephrocalcinosis	DNA study	PubMed (38)
Primary amyloidosis (2)	Systemic	Nephrotic syndrome	Biopsy	PubMed (39)
WAGR syndrome (1)	Syndromatic	Wilms TU, renal cysts	FISH	PubMed (accepted) (40)
Wegener granulomatosis (2)	Systemic	Glomerulonephritis	Biopsy	PubMed (41, 42)
Good pasture syndrome (3)	Pulmorenal	Crescentic nephritis, CRF	Biopsy	unreported

CRF – chronic renal failure, TIN – tubulointerstitial nephritis, NA – data not available

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Резиме

РЕТКИ БОЛЕСТИ СО ЗАСЕГАЊЕ НА БУБРЕЗИТЕ И УРИНАРНИОТ ТРАКТ ВО РЕПУБЛИКА МАКЕДОНИЈА

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Апстракт: Ретките болести се голем проблем за пациентите и нивните семејства, бидејќи често не се препознавани од страна на медицинските експерти. Дополнителен проблем е и фактот дека здравствените фондови, поради ограничените средства, често одбегнуваат да ги преземат своите одговорности за пациентите со РБ. Нивниот голем број (5–8000), како и големиот број болни со РБ (6–8% од популацијата) се предизвик за секое општество, но особено за земјите во развој. Истовремено, за науката РБ се непроценлив извор на нови сознанија од областа на фундаменталните биолошки закони. Целта на овој труд е подобар преглед на состојбата со РБ кои ги засегаат бубрезите и уринарниот тракт (РББУТ) во Република Македонија. Како извор на увид користен е PubMed Central и трудовите кои во оваа база на податоци се објавени од страна на македонските автори. Во одделни случаи (но не и сеопфатно) употребивме и податоци од локални извори. Се покажа дека постои значителен број на РББУТ кои се публикувани во списанија регистрирани на PubMed, и особено значително, во списанија со импакт фактор. Фактот дека постојат значителни публикации за овој проблем, докажува дека во Македонија постои стручна свест и професио-

нална компетентност за дијагностицирање, и во случаите каде што постои лекување и за овие болести. Сепак, според преваленциите објавени во развиените земји, сметаме дека е јасно дека РББУТ во недоволен број се дијагностицирани во нашата земја. На пример, сè уште не постои пациент кај кој е дијагностицирана Фабриева болест, иако според објавените податоци за преваленција на оваа болест, Македонија би требало да има вакви пациенти. Од научен аспект е потребно да се истакне дека некои од трудовите на македонските автори, се поместени во корпусот на фундаменталните медицински познавања. Сето тоа е осведочено со важен број на трудови објавени во списанија со значителен импакт фактор.

Заклучоци: Потребно е зголемување на будноста, но и нови форми на доедукација за лекарите. Здравствениот фонд на Македонија мора да ги опфати и овие пациенти во финансирање на дијагностицирање и лекување на овие болести. Воведување на широк неонатален скрининг (триесетина наместо една болест) е исто така нужност.

Потребно е и понатамошно поддржување на невладините организации на пациентите во нивната активност за подобрување на грижата на пациентите со ретки болести.

Клучни зборови: ретки болести, Македонија, бубрези, уринарни патишта, генетика.

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