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Minireview

Renal involvement in PMM2-CDG, a mini-review

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ABSTRACT

Phosphomannomutase 2 deficiency (PMM2-CDG) is the most common N-linked glycosylation disorder. The majority of patients present with a multisystem phenotype, including central nervous system involvement, hepatopathy, gastrointestinal and cardiac symptoms, endocrine dysfunction and abnormal coagulation. Renal abnormalities including congenital malformations and altered renal function are part of the multisystem manifestations of congenital disorders of glycosylation.

We reviewed the literature on 933 patients with molecularly and/or enzymatically confirmed PMM2 deficiency to evaluate the incidence of renal involvement in PMM2-CDG.

Renal abnormalities were reported in 56 patients. Congenital abnormalities were present in 41 out of these 55. Cystic kidney and mild proteinuria were the most common findings. One of the most severe renal manifestations, congenital nephrotic syndrome, was detected in 6 children. Renal manifestations were not associated with the presence of specific PMM2 alleles.

This review summarizes the reported renal abnormalities in PMM2-CDG and draws attention to the pathophysiological impact of abnormal glycosylation on kidney structure and function.

1. Introduction

Congenital disorders of glycosylation (CDG) are a rapidly expanding group of metabolic disorders. Mutations in the glycosylation pathway affect a high number of structural and functional glycoproteins and lead to multiple organ system involvement in most patients with CDG. PMM2-CDG is the most common N-linked glycosylation defect. It is a multisystem disorder with variable severity and important clinical heterogeneity among affected individuals. Almost any organ/system can be involved in PMM2-CDG. The phenotypic spectrum is thus very broad ranging from lethal hydrops foetalis to a mild neurological form without prominent multisystem involvement in adulthood.

Renal involvement in congenital disorders of glycosylation has not been systemically studied and its pathophysiology is not fully understood. In early 1991, cystic kidney and tubular proteinuria were the first two renal manifestations described in individuals with a PMM2-CDG phenotype (called carbohydrate-deficient glycoprotein syndrome

type I at that time) [1,2,3]. These first reports raised attention for possible renal involvement in CDG as part of the multisystem involvement. We here present a literature review on the occurrence of renal abnormalities, and the specific types of renal involvement in PMM2-CDG.

2. Methods

A PubMed database search was performed using the following terms: Congenital disorder(s) of glycosylation, type Ia OR PMM2 OR PMM2-CDG OR phosphomannomutase 2 deficiency OR Jaeken syndrome plus Kidney OR Renal failure OR Anomaly OR Cyst OR Malformation OR Dysplasia OR Tubulopathy OR Fanconi OR Aminoaciduria OR Renal tubular Acidosis OR Proteinuria OR Nephrosis. All the publications were included in the search from the time of the disorder discovery, i.e. 1980. All the patients with confirmed with biallelic *PMM2* mutations, or enzymatically confirmed

Abbreviations: PMM2, phosphomannomutase 2; CDG, congenital disorder(s) of glycosylation; ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease

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Table 1

Summary of the renal findings in previously reported PMM2-CDG patients.

Year, Reference No.	No. of patients per report	Age at publication	Main renal manifestation	US/biopsy/Autopsy	Patient's outcome	Early infantile type
1995 [4]	1	3 m	Nephrotic syndrome (protein/creatinine 1337 mg/mmol) Hypoalbuminemia aminoaciduria	NA	Died at 3 months	Yes
1996 [5]	1	2 w	Nephrotic syndrome (protein/creatinine 1113 mg/mmol) hypoalbuminemia aminoaciduria high serum creatinine	US: Enlarged kidneys Biopsy: diffuse increase in mesangial matrix, minimal proliferation of mesangial cells, microcystic dilatation of the tubuli, hyaline casts in the tubular lumen	Died at 2 months	Yes
1998 [6]	1	8 y	Proteinuria	NA	Alive	yes
1998 [7]	1	1 y	Tubular Proteinuria	NA	Alive	No*
2000 [8]	1	10 m	NA	US: Renal cysts	NA	No
2001 [9]	11	15 m	Tubulopathy	US: Renal cysts	Alive	Yes
		6 m	Tubulopathy	US: Normal	Alive	Yes
		7 m	NA	US: Renal cysts	Alive	Yes
		10 d	NA	US: Renal cysts	Died at 18 months	Yes
		1 m	NA	US: Renal cysts	Alive	Yes
		4 m	NA	US: Renal cysts	Alive	Yes
		3 m	Tubulopathy	US: Renal cysts	Alive	Yes
		12 m	Tubulopathy	US: Renal cysts	Died	Yes
		3 d	Tubulopathy	US: Renal cysts	Died	Yes
		5 m	NA	US: Renal cysts	Died	Yes
		3.5 m	NA	US: Renal cysts	Died	Yes
2002 [10]	1	2.5 y	NA	Echogenic kidney Renal cyst	Alive	Yes
2002 [11]	1	10 m	High creatinine Acute renal failure	US: NA	Alive	Yes
2005 [12]	1	8 w	Mild proteinuria	US: NA Autopsy: enlarged kidney, tubular dilatations with accumulation of amorphous material	Died at 8 weeks	Yes
2005 [13]	1	Birth	NA	US: NA Autopsy: enlarged polycystic kidneys	Died at 8 weeks	Yes
2006 [14]**	7	3 m	Tubulopathy	US: Inc. echogenicity Dec. corticomedullary differentiation biopsy: cortical tubular microcysts	Alive	Yes
		15 m	Tubulopathy	US: Inc. echogenicity Inc.corticomedullary differentiation	Alive	Yes
		3 d	Tubulopathy	US: Inc. echogenicity Dec.corticomedullary differentiation	Alive	Yes
		1 m	NA	US: Inc. echogenicity Inc.corticomedullary differentiation	Alive	Yes
		10 d	NA	US: Enlarged kidneys Inc. echogenicity Inc.corticomedullary differentiation	Alive	Yes
		4 m	NA	US: Enlarged kidneys Inc. echogenicity Dec. corticomedullary differentiation	Alive	Yes
2006 [15]	1	6 m	Tubulopathy	US: Normal	Alive	No
		Birth	NA	US: NA Autopsy: Dystrophic calcification in the renal tubules	Stillbirth	Yes
2007 [16]	1	5 m	Proteinuria	US: Altered echography	Alive	Yes
2007 [17]	1	8 w	NA	US: Dilatation of renal pelvis Inc. echogenicity	died at 8 weeks	Yes
2007 [18]	1	8w	NA	US: Enlarged kidneys Inc. echogenicity Autopsy: tubular cysts	died at 8 weeks	Yes
2008 [19]	1	Birth	Nephrotic syndrome (no details)	US: Inc. echogenicity	Died at 3 week	Yes
2008 [20]	1	Neonate	Renal tubular dysfunction	NA	Died	Yes
2009 [21]	1	3 m	Nephrotic syndrome (coexisting CMV infection)	US: Inc. echogenicity Autopsy: inflammatory infiltration	Died at 3 m	Yes
2009 [22]	1	Neonate	Renal tubular dysfunction	NA	Alive	Yes
2009 [23]	1	Neonate	NA	US: Enlarged kidneys cortical tubular microcysts	Died at 29 days	Yes
2010 [24]	1	Antenatal	NA	US: NA biopsy: renal tubulocystic changes in the cortex and medulla	terminated at 33.5 weeks	Yes
2014 [25]	1	7 m	NA	US: Inc. echogenicity	NA	Yes
2014 [26]	1	6 m	NA	US: Inc. echogenicity	died at 6 months	Yes
2014 [27]	1	4 y	Proteinuria	NA	Alive	Yes
2014 [28]	1	8 m	NA	US: multicystic kidney	Died at 8 months	Yes

(continued on next page)

Table 1 (continued)

Year, Reference No.	No. of patients per report	Age at publication	Main renal manifestation	US/biopsy/Autopsy	Patient's outcome	Early infantile type
2015 [29]	2	8 m	NA	US: Inc. cortical echogenicity	NA	Yes
		38 m	NA	US: Inc. cortical echogenicity	NA	Yes
2015 [30]	2	8y	NA	US: Inc. echogenicity	Alive	No
		16 y	Proteinuria	NA	Alive	No
2017 [31]	6	14 y	Tubulopathy	US: Inc. echogenicity	Alive	No
		6 y	NA	US: Inc. echogenicity	Alive	No
		15 y	NA	US: Inc. echogenicity	Alive	No
		3 y	NA	US: Inc. echogenicity	Alive	No
		1y	Tubulopathy	US: Inc. echogenicity	Alive	Yes
		1y	NA	US: Inc. echogenicity	Alive	No
2017 [32]	4	NA	Nephrotic syndrome ($n = 2$) Proximal tubulopathy ($n = 2$)	NA	NA	NA

Abbreviations: d: day, w: week, m: month, y: year, NA: not available, US: ultrasound, Inc.: Increase, Dec.: Decrease.

* Late infantile/childhood type.

** Tubulopathy described as a generalized in this report (proteinuria, calciuria, bicarbonate loss and beta-2-microglobulinuria).

phosphomannomutase 2 deficiency were included.

3. Results

We retrieved 165 peer-reviewed publications on PMM2-CDG and identified 29 papers reporting on renal involvement.

From 933 PMM2-CDG individuals described so far, not prospectively and systematically tested for renal involvement, only 6% ($n = 55$) were reported to be affected with structural and/or functional renal abnormalities; nineteen males, twenty females and the gender was not available for sixteen individuals (Table 1).

3.1. Structural anomalies

Cystic kidneys were reported in nineteen individuals (thirteen detected by renal ultrasound, three by renal biopsy and three by autopsy). The most common ultrasound finding was increased renal echogenicity ($n = 23$), followed by enlarged kidney size ($n = 7$), alteration of the corticomedullary differentiation; either increased corticomedullary differentiation ($n = 3$) or decreased corticomedullary differentiation ($n = 3$).

Less frequent abnormalities i.e. renal pelvis dilatation and tubular dilatation were reported in two individuals (Table 1).

3.2. Abnormal renal function

Proteinuria has been reported in twenty-one individuals, including non-classified proteinuria ($n = 5$). Tubular proteinuria was reported in sixteen individuals where four of them had generalized tubulopathy with hypercalciuria, low molecular weight proteinuria and aminoaciduria. The tubulopathy was associated with abnormal renal ultrasound in eleven individuals, while normal ultrasounds were reported in two individuals and were not available for eight individuals.

The data about the renal function in 29 individuals reported with abnormal renal ultrasound, biopsy and/or autopsy were not available.

Increased serum creatinine was reported in only two individuals; one presented with acute renal failure and myocardial ischemia, and the other with severe nephrotic syndrome and rapid deterioration of renal function.

Nephrotic range proteinuria was reported in six individuals. Data were available for four of them showing that all presented within the first month of life and died within the first three months of life (data not available for the other two patients); the protein/creatinine ratio was reported in only two patients (all in nephrotic range). Renal biopsy in one patient showed diffuse mesangial sclerosis (Table 1).

3.3. Onset of renal manifestations in PMM2-CDG

Most of the renal findings were reported in the severe early infantile type ($n = 41$). The median age at diagnosis of renal involvement in this type was three months.

Non-progressive renal anomalies, mainly abnormal kidney echogenicity, and mild proteinuria were found in only eleven individuals with the late infantile/childhood neurological type. The median age at diagnosis of renal involvement in this type was three years. The age at onset was not known for 4 patients.

Data about the renal function in individuals with congenital renal anomalies and the presence of tubulopathy were usually lacking. Most of the reported findings were listed briefly as a part of the PMM2-CDG clinical presentation. The impact of those renal abnormalities on the renal function e.g. progression of the renal involvement is unknown, due to lack of follow up data of the surviving individuals. About 46% ($n = 19/39$) of the patients with the early infantile form expired.

4. Discussion

Literature review revealed that the renal involvement is more frequently reported in the severe infantile form of PMM2-CDG compared to the milder childhood onset form. However, in several reports on PMM2-CDG patients no specific information is available on renal involvement.

Renal cysts are present in many genetic disorders including, but not limited to autosomal dominant and recessive polycystic kidney disease, nephronophthisis, medullary cystic kidney disease, and tuberous sclerosis. Additionally, cystic (dysplastic) kidneys have been described in metabolic disorders such as peroxisomal disease, mitochondrial cytopathies and congenital disorders of glycosylation subtypes; PMM2-CDG, ALG9-CDG, ALG6-CDG, CDG-Ix and GANAB-CDG [33,34,35].

The mechanisms involved in the cystic kidney development are not well understood. Animal studies revealed a very complex kidney developmental process requiring different molecular mediators to ensure normal kidney structure. Glycosylation plays a critical role in the biogenesis and function of many membrane proteins that are involved in fetal kidney development. Proteoglycans are already present in the mesoderm and they have an important role in modulating the tubule inductive signals along with the integrins, which are also mainly glycoproteins. They bind to several components of the extracellular membrane (ECM) that control cell adhesion. The morphogenesis process is completed by the extracellular matrix components which are important for polarization of the epithelial tubule during the organogenesis. The glycoproteins in other specialized structures such as the basement membrane form an adhesive support for differentiating and

migrating kidney cells and can also form physical barriers limiting cell–cell interactions [36]. Animal studies indicate that mature glycosylation reflects the functional maturation of the adult nephron. This was concluded from measuring the lectin attachment to saccharides in different embryonic nephrons (podocytes, proximal and distal tubules and the collecting ducts) [37].

Many membrane proteins are glycoproteins including the Transient Receptor Potential channel (TRPP) which is a nonselective cation channel and heavily N-glycosylated. Two important glycoproteins, polycystin-1 (TRPP1), and polycystin-2 (TRPP2) are involved in multiple signaling pathways to maintain normal renal tubular structure and function. Defective glycosylation could disrupt the function of both glycoproteins and lead to cystic formation in kidneys similar to autosomal dominant and recessive polycystic kidney diseases (ADPKD, ARPKD) [38]. Additionally, hypoglycosylation affects the biogenesis and stability of the PKD2 protein which could contribute to the pathogenesis of ADPKD [39].

GANAB gene encodes the alpha subunit of glucosidase II, which plays a role in protein folding and quality control by cleaving glucose residues from immature glycoproteins in the endoplasmic reticulum. Glucosidase II α subunit (GANAB) deficiency was recently added to the endoplasmic reticulum related CDG types (GANAB-CDG) with a phenotype resembling polycystic kidney disease, mainly enlarged kidneys and multiple cysts [34,40].

The specific role of PMM2 in renal morphogenesis is not well studied. Considering that PMM2 is involved in the early step of glycoprotein biosynthesis, mutations in PMM2 subsequently affect glycosylation through many proteins involved in kidney organogenesis. A trial with prenatal oral mannose supplement in heterozygous *PMM2* female mice showed normalization of the glycosylation pattern in the homozygous *PMM2* mice products and normal morphology of different organ tissue including heart, liver, lung, kidney, thymus, spleen and brain tissue compared to the homozygous *PMM2* mice that did not receive prenatal mannose and showed hypoglycosylation and multiple organ degradation which leads to lethality. This highlights the role of mannose in rescuing the N-linked glycoproteins during the embryonic development, which could prevent the congenital malformations [41].

A recent publication further supports the role of PMM2 in kidney morphogenesis. A promoter mutation in *PMM2* in seventeen patients (not included in the table) presented with a remarkable phenotype of hyperinsulinemia and polycystic kidney disease with variable severity, ranging from asymptomatic cysts to end stage renal disease [42].

Normal renal parenchyma on ultrasound is less echogenic than the liver and spleen except in neonates and young children, where the echogenicity may be similar to these organs. Increased renal echogenicity is seen in several conditions including polycystic kidneys [43]. In PMM2-CDG, increase renal echogenicity was the most common ultrasound finding, which could indicate underlining microcystic abnormality of the kidneys [14].

Proteinuria may represent a benign condition or a serious underlying renal disease; either from glomerular or tubular dysfunction [44]. In the current literature on PMM2-CDG the type of proteinuria was only documented in sixteen individuals (tubular dysfunction). Congenital nephrotic syndrome (CNS) is defined by the presence of nephrotic-range proteinuria (protein excretion of more than 40 mg/m²/h or a first-morning urine protein/creatinine of 2–3 mg/mg creatinine or greater), edema, hyperlipidemia, and hypoalbuminemia with the onset within the first three months of life [45]. In PMM2-CDG, six individuals have been reported with biochemical phenotypes of nephrotic syndrome. Although tubular involvement is reported more frequently in PMM2-CDG, nephrosis in PMM2-CDG indicates disturbed glomerular function. This could occur due to abnormal synthesis of proteoglycans, important for the glomerular barrier, cell signaling, anchorage of cells to the glomerular basement membrane and podocyte morphology [46].

Our literature review did not reveal any disorder-specific management for renal dysfunction in PMM2-CDG patients. The outcome of

renal dysfunction correlates with the severity and the onset of PMM2-CDG; as most of the reported individuals with severe early multisystem form had the poorest outcome.

In conclusion we suggest adding PMM2-CDG to the metabolic differential diagnosis of cystic kidneys, hyper-echogenic kidneys, tubular proteinuria and/or congenital nephrotic syndrome in infants and children, especially when these are present as a multisystem disorder. Biochemical screening (e.g. transferrin isoelectrofocusing) should be followed by *PMM2* molecular testing, especially in case of neurologic involvement. On the other hand, any newly diagnosed PMM2-CDG patient should be subjected to a renal investigation including blood pressure, serum creatinine, urea, electrolytes, urine analysis (proteins, amino acids, calcium, phosphate), and a base-line renal ultrasound.

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