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Management of polycystic kidney before and after transplantation

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Autosomal dominant polycystic kidney disease (ADPKD), the most common inherited ciliopathy kidney disease cause end stage renal disease worldwide characterized by relentless growth and enlargement of kidney cysts causing progressive kidney size enlargement, associated with hypertension, nephrolithiasis, cyst hemorrhage and infections. In Thailand, ADPKD is the fourth most common cause of renal replacement therapy next to diabetes mellitus, chronic glomerulopathy, and obstructive nephropathy. Recent advances in molecular genetics and pathophysiology of ciliopathy facilitate the diagnosis and management of the disease. However, there are remain uncertainties of ADPKD patient evaluation and patient management to delay progression of renal function and extra-renal manifestations. The differences of PKD 1 gene and PKD 2 gene, the heterogeneity of PKD 1 gene and PKD 2 gene, and the epigenetic or second hit in each individual case cause variation of clinical course, progression and prognosis. Recent studies have showed that non-truncating allele of PKD 1 associated with less progressive manifestation compared with truncating mutations. Although there are gaps of knowledge of the ADPKD genome variation in different ethnics, it has been certain that the variations exist among ethnicities and guideline for management in a race may not be appropriately applied to other races. Gross hematuria and cyst hemorrhage, nephrolithiasis, cyst infection and chronic pain are major renal complications of ADPKD. These complications are associated with progression of kidney function and indicate unfavorable prognosis lead to end stage renal disease require renal replacement therapy. Intra-cranial aneurysms and ruptured intra-cranial aneurysms are major extra-renal complications. Indications for intra-cranial aneurysms screening include family history of intra-cranial aneurysms and subarachnoid hemorrhage. Risk of renal cell carcinoma in ADPKD patients does not increase compared with that in patients with other chronic kidney diseases and no specific recommendation for renal cell carcinoma screening required.

Molecular genetic testing is not routinely recommended for diagnosis of ADPKD cases at this time, however, genetic testing should be used for atypical case presentations such as sporadic polycystic kidney without family history, markedly asymmetric polycystic kidney, progressive declination of kidney function without marked cystic enlargement, or stable kidney function with progressive cystic kidney enlargement. Studies have shown total kidney volume by computed tomography, and magnetic resonance imaging in relation to age identify patients with progressive decline of kidney function. Total kidney volume measurement should be accessed by validated assessment protocol whenever novel medication interventions are planned to prescribe for the patients, to monitor efficacy of the intervention since change of renal function is an insensitive surrogate marker especially for early ADPKD cases. Change of estimated glomerular filtration rate of ADPKD requires long term follow up to evaluate the treatment efficacy.

Management of ADPKD includes control of hypertension and novel medical interventions. Renin-angiotensin-aldosterone system (RAAS) blockage should be used as the first-line medication with strict low salt diet. Understanding of pathophysiology of cyst progression and declination of kidney function bring novel medical interventions of ADPKD. Antidiuretic hormone arginine vasopressin has been shown as key biomechanistic progression of disease and clinical studies revealed arginine vasopressin V2 receptor antagonist slow down the rate of total kidney volume growth and rate of estimated glomerular filtration rate declination in ADPKD patients. For management of ADPKD cystic infection, lipid-permeable anti-microbial agents, fluoroquinolones and trimethoprim-sulfamethoxazole are recommended antibiotic. If infections are intractable to medical treatment, drainage of infected

cyst is needed by intervention procedure.

Kidney transplantation is the renal replacement therapy of choice for ADPKD. Pre-emptive living related kidney transplantation should be considered if kidney donor is available. Although mitral valve prolapse and colonic diverticular are not clinically significant extra-renal manifestation of ADPKD, complete cardiovascular and gastrointestinal evaluation are recommended for pre-transplantation recipient evaluation. Native kidney nephrectomy has not been routinely recommended prior to transplantation, as nephrectomy in ADPKD patients is associated with significant morbidity and mortality. However, native kidney nephrectomy should be considered in ADPKD patients with recurrent cyst infection, symptomatic nephrolithiasis, recurrent bleeding cyst or severe cystic bleeding, chronic intractable pain and severe hypertension unable to be adequately controlled with anti-hypertensive medications. Registry data showed that there are no significant differences of patient's survival and renal allograft survival of ADPKD patients compared with non-diabetic kidney transplant recipients. Chronic hemodialysis and chronic ambulatory peritoneal dialysis are renal replacement therapies of ADPKD patients who are not candidate for kidney transplantation. Chronic ambulatory peritoneal dialysis is not a contraindication for ADPKD, however, adequate intra-peritoneal volume should be considered before initiate the treatment.

In summary, advance genomic methodology allows accurate and precise diagnosis of ADPKD, the study of genomic mutation of ADPKD correlated with clinical progression and outcome in the future will provide precision medicine for early treatment of the disease and will establish individualized tailor-made therapy to delay CKD progression and prevent end stage renal disease. Specific pre-kidney transplantation evaluations in addition to the evaluation of non-ADPKD recipient require to prevent post-transplantation complications. Pre-transplantation native kidney nephrectomy or simultaneous native kidney nephrectomy in selected cases may prevent post-transplantation morbidities.