Polycystic Kidney Disease in a Patient Using Lithium Chronically

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SUMMARY

Lithium remains to be the gold standard in the treatment of mood disorders. This study presents a case treated with lithium for an extended period with a good response. Following an increase in creatinine levels, further investigation of renal dysfunction revealed polycystic kidney disease. Lithium was used prior to the diagnosis of polycystic kidney disease, resulting in the unique opportunity to examine the effects of lithium on kidneys with polycystic kidney disease. Within this context, this study also discusses the pharmacokinetics of lithium, and its possible relation to cyst formation in polycystic kidney disease.

Keywords: Bipolar disorder, lithium, polycystic kidney disease

INTRODUCTION

Lithium is an effective and reliable medicine that has been used in the treatment of bipolar disorder for many years. However, it can negatively affect renal functions, resulting in nephrogenic diabetes insipidus, tubule-interstitial nephritis, and nephrotic syndrome (Kripalani et al. 2009). Lithium decreases the vasopressin response of collecting tubules by interrupting the function of Aquaporin-2 channels. Therefore, lithium decreases the urine concentrating function of the kidneys and leads to polyuria. Prolonged periods of medication result in decreases in the concentration ability of the tubuli, and therefore an accumulation of glycogen and distention in the epithelium (Goodwin and Jamison 2007). In chronic applications, microcysts up to 1-2 mm may be observed (Tuazon et al. 2008). Acute intoxication and polypharmacy, and other coexisting general medical conditions are risk factors for renal complications in patients using lithium (Gitlin 1999).

The frequency of Polycystic Kidney Disease (PKD) ranges between 1 and 2 per 1000 live births (the most frequently seen genetic disease) and the disease is related to mutations in the PKD1 and PKD2 genes (Bisceglia et al. 2006, Murcia et al. 1999). After cystogenesis is completed, the cysts are separated from other parts of the nephron and tubuli and do not affect parenchyma (Murcia et al. 1999). Therefore, 9 out of 10 individuals with PKD can live healthy lives without experiencing negative effects on rental functions (Bisceglia et al. 2006).

Current recommendations on lithium usage do not include exact instructions in cases of renal problems. A literature survey determined that there are few studies available regarding lithium usage in PKD, and only one study reports a case of lithium use in PKD (Shahetal 2010). The results of lithium usage in PKD were experimentally examined after the patient used lithium while unaware of the presence of PKD disease. In this process, the subject her/himself administered and ceased lithium by her/his own decision, these processes may demonstrate effects of administration and ceasing lithium. The administration of lithium was immediately ceased upon diagnosis of PKD. The authors evaluated this case as an experiment on processes of ceasing or beginning lithium in PKD. The study present a patient who had been using lithium for an

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extended period and who was diagnosed as autosomal dominant PKD during an examination to determine the cause of induced creatinine levels. This case report also includes a survey of the literature on lithium usage in PKD.

CASE

Mr. A is 44 years old, has worked in different jobs for short periods in the past and has been working at the same place for a year. Bipolar disorder began when she/he was 16 years old (in 1983), however before the disease she/he had problems such as lack of attention in school, introversion, desire to be alone, headaches, difficult sleeping, emotional fluctuations and boredom. She/he had experienced 8 disease periods and had attempted suicide six times throughout her/his life. After a mania period she/he passed through in 1987, lithium and an antipsychotic were administered. Subsequently, lithium and risperidone were administered and she/he achieved in remission for ten years with treatment. During a mania period in 1997, sodium-valproate (1500 mg/day) was added to the lithium (1200 mg/day) treatment, which continued for the next 11 years. In 2009, it was decided to decrease and cease lithium following the rise in polyuria, polydipsia and serum creatinine values and an antipscyhotic were prescribed. Table 1 shows blood lithium, creatinine and urea values measured during monitoring of the patient at the authors' clinic.

Table 1. Laboratory results from the patient's clinical course

Date	Serum Lithium Level (mmol/L)	Daily Lithium Dosage (mg/day)	Creatinine (mg/dl)	Urea (mg/dl)
May 2008	1.14	900	1.4	32
July 2008	0.93	900	-	-
September 2008	0.77	900	1.6	42
September 2008	1.31	600	-	-
October 2008	1.04	300	-	-
November 2008	1.01	300	1.8	27
December 2008	0.40	300*	0.8	18
June 2009	-	-	1.7	42
January 2011	1.5	900	2.1	49
February 2011	1.03	900	2.2	51
March 2011	-	300	1.7	43
April 2011	-	-	1.7	44
June 2011	-	-	2.0	51
July 2011	-	-	1.9	38
September 2011	-	-	1.7	26
May 2012	-	-	2.06	49
September 2012	-	-	2.44	58

*The dosage decreased starting in in September 2011 and the lithium was completely ceased in January 2011.

After the commencement of valproate, the patient started to complain of sexual reluctance, for which she/he blamed valproate. The patient consulted the urology department regarding her/his sexual complaints in December 2010. Venous stasis was detected in penile Doppler ultrasound, and this problem was resolved by surgical operation. The patient stated on January 2011 that she/he was using lithium instead of valproate in order to avoid sexual problems. Following laboratory results reporting the creatinine value as 2.1 mg/dl, and the urea value as 49 mg/dl, it was recommended to cease lithium and resume valproate. She/he was referred to the nephrology department.

Laboratory analysis revealed an urea value of 51 mg/dl, creatinine as 2.9 mg/dl, BUN as 24 mg/dl (normal range: 5-20), and uric acid as 8.6 mg/dl (normal range: 3.5-8.5) in June 2011. The urine analysis was found to be normal and proteinuria was not detected. In addition, the abdominal ultrasonography reported grade 1 hepatic steatosis, slight growth of both kidneys, and the existence of many irregular localized (scattered in cortex and medulla) anechoic cysts. A hypoechoic nodule of 36×34 mm size was detected, suggesting the existence of a complicated cyst at the lower pole of the left kidney. The parenchyma tissue and the pelvicaliceal system had a normal appearance. The contrast abdominal MRI analysis (July 2011) revealed many scattered cysts in both kidneys. However, the cyst shapes suggested that they were not malignant. When evaluated together with the ultrasound, the cystic lesion with dense content was determined to have resulted from blood components. As a result of these examinations and analysis, the patient was diagnosed with autosomal dominant polycystic kidney disease. The diagnosis was supported by the known PKD histories of her/his family (her/his father and uncle). In the colonoscopy conducted in August 2011 due to her/his chronic constipation complaints, hemorrhoids, polyposis, and diverticulosis were detected and polypectomy was applied during colonoscopy. In addition, secondary symptoms, frequently observed in polycystic kidney disease, including hypertension, cerebral aneurysm, and valvular heart disease, were not detected during internal medicine, ophthalmic, and neurology consultations. There was insufficient information regarding creatinine levels in the patient before 2008. The patient reported that routine examination results were within normal ranges. Creatinine values rose in 2009 and receded to normal levels after ceasing lithium administration in 2009. The creatinine value increased after restarting lithium usage in 2011. The creatinine levels did not recede to normal levels after ceasing lithium. Lithium usage

and serum levels were correlated with the increase in creatinine levels, and lithium likely had both acute and chronic toxic effects on the kidneys. After ceasing lithium, valproate at 1500 mg/day dosage and Aripiprazole at 15 mg/day dosage were started. This treatment has continued since 2011. The patient stayed remitted (euthymic) since ceasing lithium.

DISCUSSION

Long-term lithium usage can lead to chronic interstitial nephrite induced chronic kidney disease in 15-20% of patients (Kripalani et al. 2009). Microcysts up to 1-2 mm at distal tubuli and collecting tubuli have been observed following lithium usage (Tuazon et al. 2008). Since the patient had many macroscopic cysts, the largest of which were 24 and 25 mm, these cysts were an indicator of possible PKD cysts at diagnosis. It was impossible to determine the fluctuation of creatinine levels in this patient due to limitations in her/his medical history. Table 1 shows a rare increase in creatinine levels occurring in the patient during the period when she/he used lithium. However, glomerular filtration rate is a better indicator of renal functions in lithium users rather than creatinine levels. Another interesting aspect of this case was the parallel increase of the creatinine and serum levels of lithium (table 1), which may suggest a relationship between creatinine levels and toxic levels of lithium; or in other words a vulnerability to lithium overdose.

The cysts observed in polycystic kidney disease have both biological and genetic origins. Anomalies at the systemic (macro) and cell (micro) level are expected in PKD, and these anomalies may affect all organs and systems. Our patient did not have secondary manifestations of PKD in other systems. However, several factors may affect pharmacokinetics and pharmacodynamics of lithium by the physiopathology of PKD. Lithium enters into the cell at the depolarization phase via the Na/K-ATPase pump and voltage-gated sodium channels (El-Mallakh 1992). Disorders in the physiology of the Na/K-ATPase ion channel in the erythrocytes have been observed (Vareesangthip et al. 1998) in PKD, and these abnormalities in the Na/K-ATPase pump are thought to occur systemically. In addition to ion channel pathologies, PKD was determined to increase intracellular cAMP levels in the kidney, liver, vascular smooth muscle, and choroids plexus in animal models (Basinz et al. 2007, Masyuk et al. 2007). The mechanism of ion channel inhibition has not been determined, however lithium is known to decrease adenylate cyclase activity and thus cAMP levels. Liquid secretion results from the activation of the adenylate cyclase signaling pathway in single-layer cultures of cystic PKD epithelium (Ye and Grantham 1993). Moreover, anomalies in the Na/K-ATPase pump also contribute to cystogenesis (Wilson et al. 1991). The Wnt signaling pathway is important in normal renal development and excessive Wnt activation has been shown to cause PKD in animal models (Benzing et al. 2007). It is not known whether Wnt activation contributes to PKD pathophysiology in humans. Lithium increases the activity of the Wnt pathway, that may suggest a possible pathway by which lithium may encourage cystogenesis.

Although there is not sufficient data on the pathophysiological processes of PKD or the effect of lithium on PKD, it is possible to speculate that malfunctions of lithium intake through neuron membranes (or through blood-brain barrier) may render lithium ineffective even if there is sufficient lithium concentration in the brain. It should be further investigated. The potential harmful effects of lithium on cyst formation and other processes in PKD should be considered and lithium should not be used to treat bipolar disorder in individuals with PKD. It should be noted that renal elimination of carbamazapine and valproate may be decelerated therefore may require attention in cases of renal failure. Similarly, for other psychotropic medications, elimination problems through kidneys and potential interactions with pathological processes of PKD should be considered.

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