Peer Review File

Article information: http://dx.doi.org/10.21037/tp-20-476

Reviewer A

Comment 1: In line 115, you mention pathology and bone puncture. By pathology do you mean pituitary biopsy? And what is bone puncture? Is it another biopsy from elsewhere? Please elaborate the details.

Reply 1: Thanks for your valuable suggestion. We must admit that we have not described correctly and in detail in the previous manuscript. Pathology means bone biopsy, as the cranial computed tomography showed bone destruction; bone biopsy was performed and it revealed fibrous adipose tissue and focal inflammatory cell infiltration. We have modified our text as advised (see Page 6-7, lines 120-123). In the revised version, the "bone puncture" has been corrected as "bone marrow biopsy" (see Page 7, line 123).

Changes in the text: See Page 6-7, lines 120-123 (marked in red).

Comment 2: Did the patient go through another water deprivation test the second time?

Reply 2: Thanks for your valuable suggestion. The patient did not go through another water deprivation test. As repeated pituitary MRI showed the pituitary stalk thickening and cranial computed tomography showed bone destruction, the results were consistent with central diabetes insipidus induced by Langerhans cell hyperplasia. In addition, the treatment was effective. We added some information in our text to explain (see Page 6-7, lines 120-126). But as suggested by reviewer, we agree that it was better to go through another water deprivation test.

Changes in the text: See Page 6-7, lines 120-126 (marked in red).

Comment 3: In line 117, you mention treatment was performed. Did the patient receive treatment for DI e.g Desmopressin? Only details of the surgical treatment of hydro nephrosis is described.

Reply 3: Thanks for your valuable suggestion. We have re-written this part in detail according to your suggestion. Desmopressin was administrated according to urine volume for DI and glucocorticoid and chemotherapy were given for Langerhans cell hyperplasia. Polydipsia improved significantly with above treatment. We have modified our text as advised (see Page 7, lines 125-126).
Changes in the text: See Page 7, lines 125-126 (marked in red).

Reviewer B: The Manuscript "Asymptomatic obstructive hydronephrosis associated with diabetes 1 insipidus: a case report and review" describes a very interesting and rare case. The author's use the case report as a good opportunity to discuss the complexity of the follow-up of an infant or child with the prenatal diagnose of hydronephrosis and how others factors can change the therapeutic approach, including diseases and physiological processes related to polydipsia/ polyuria.
In my opinion, this is a relevant topic to discuss. However, there are a few points in the cases presentation and discussion that in my opinion should be addressed in order to improve the manuscript.
Comment 1: Abstract - If we have the follow up on the hydronephrotic kidney function after the surgery will be interesting to have the information added to the abstract (see comment below).
Reply 1: Thanks for your valuable suggestion. It is really true as you suggested that the follow up on the hydronephrotic kidney function after the surgery is very important. Usually in our protocol, it is recommended to go through another diuretic renography (DR) to evaluate the renal function and kidney scar after surgery. However, this patient did not have repeated DR to evaluate his postoperative renal function. The detailed explanation is in the part of reply for comment 3.

Comment 2: Case presentation - Line 88 and 89 "... significantly worsening left hydronephrosis with an APD of 6.25cm at the follow-up renal ultrasound..." and

lines 95/96 “Renal ultrasound showed severe hydronephrosis with an APD of 6.25cm...” Since it shows the same measurement it would be better just to describe as “unchanged”.

Reply 2: Thanks for your valuable suggestion. The “two” ultrasound measurements you mentioned was actually the same one, which was measured initially after having polydipsia and polyuria for three months (Fig 2B). The first ultrasound measurement you mentioned is in patient’s history of present illness, while the second one you mentioned is under imaging examinations part. Considering your suggestion, we have modified this part in our text (see Page 6, lines 102-103).

Changes in the text: See Page 6, lines 102-103 (marked in red).

Comment 3: Case presentation - The most important reason to perform a follow-up in infants and children with prenatal hydronephrosis is to prevent kidney damage with scar formation and decrease of the renal function. Do you have any functional kidney evaluation after the ureteral surgery? Does the patient have any post surgical evaluation for kidney scar?

Reply 3: Thanks for your valuable suggestion. We really agree with your suggestions that the follow up on the hydronephrotic kidney function after the surgery is very important. Usually in our protocol, it is recommended to go through another diuretic renography (DR) to evaluate the renal function and kidney scar after surgery. However, this patient did not go through another DR after surgery as patient’s parents refused it for the concern of extra radiation exposure and invasive procedure. Patient’s post-operative renal function (serum creatinine and BUN etc.), serum and urine electrolyte values were within normal limits, and ultrasound showed stable APD and renal cortical thickness. In fact, the most recent renal ultrasound showed an APD of 1.8cm, this was not included in the original manuscript as the ultrasound was just done last month. We added some information about that in our text (see Page 6, lines 116-117).

Changes in the text: See Page 6, lines 116-117 (marked in red).

Comment 4: Discussion and conclusion - The paper will be improved adding more about information about the importance of the follow-up to prevent kidney damage with scar formation and decrease of the renal function.

Reply 4: Thanks for your valuable suggestion. We really agree with your suggestions that the importance of the follow-up. Prenatal ultrasound has been increasingly implemented in prenatal screening and more than 90% of pregnant women receive it. About 70% of neonates, who were diagnosed with prenatal hydronephrosis do not have clinical symptoms or signs. The identification of these asymptomatic prenatal hydronephrosis may minimize renal damage with regular follow-up. Mild hydronephrosis may be transitional and can resolve spontaneously; however, delayed intervention for obstructive hydronephrosis could affect the recovery of renal function after operation. The suitable time and exact indications for surgical intervention are complex and remain controversial. Over the past a few decades, it is a trend to choose conservative treatment for asymptomatic hydronephrosis, so regular follow-up is crucial to prevent renal dysfunction in this patient population. We added some information about that in our text (see Page 7, lines 130-139).

Changes in the text: See Page 7, lines 130-139 (marked in red). Reference 9 was inserted.

Comment 5: Discussion and conclusion - A good review of the association between hydronephrosis and polyuria was published in 1978 by Shapiro et all describing seven cases of hydronephrosis associated with different types of diabetes insipidus. (Shapiro S al. Diabetes insipidus and hydronephrosis. J Urol. 1978 Jun;119(6):715-9). Since 1978 the clinical/ surgical approach have changed a lot due to many reason including the prenatal diagnosis and clinical follow-up. How this changes have impact the preservation of the renal function will be an interesting topic to be add to the discussion.

Reply 5: Thanks for your valuable suggestion. In 1978, Shapiro et al. suggested

that persistent polyuria should be followed with serial intravenous pyelograms and renal function examinations, and surgical intervention should be reserved for cases with evidence of obstruction. In 1980s, more and more children with asymptomatic hydronephrosis were discovered by pediatricians and urologists with the implementation of fetal ultrasonography (US). As realizing that hydronephrosis can improve spontaneously with time in many cases, the initial over aggressive surgical intervention was tempered. Anteroposterior diameter (APD) and split renal function below 40% have been considered the main parameters to indicate surgical intervention (see Page 7-8, lines 140-148). In 1993, Society for Fetal Urology (SFU) proposed the importance of the thinning of the parenchyma as it can lead to decrease of the renal function. In addition, SFU grading system recommends that each grade has its own clinical follow up interval and treatment. The indications for surgical intervention: include deterioration of hydronephrosis, decline of split renal function＞10%, split renal function＜40%, obstruction curve on DR, or febrile urinary tract infection (see Page 8, lines 148-161). Patients continue to require careful monitoring after surgery if there are persistent symptoms, like polydipsia and polyuria. As you considered that the clinical/surgical approach have changed a lot due to the prenatal diagnosis and clinical follow-up. These changes play a positive role in the protection of renal function (see Page 8-9, line 164-167). With the implementation of prenatal ultrasound and regular follow-up, more and more asymptomatic hydronephrosis have been found in the early stage, as well as the changes of hydronephrosis. Surgical intervention could be performed to protect renal function if there are evidence of deterioration of hydronephrosis, or significant decline of renal function. However, when asymptomatic hydronephrosis is accompanied with persistent symptoms, like polydipsia and polyuria, even if there is no obvious change of hydronephrosis on ultrasound in the early stage, sudden aggravation of hydronephrosis and rapid decline of renal function may occur at later stage. Just like this case we presented in our manuscript. Therefore, due to protect renal function, we think that clinical approach based on prenatal diagnosis and clinical

follow-up should be adjusted in time according to examination results and clinical symptoms. We added some information about that in our text (see Page 7-9, lines 140-150 and 164-167).

Thank you again for your positive comments and valuable suggestions to improve the quality of our manuscript.

Changes in the text: See Page 7-9, lines 140-150 and 164-167 (marked in red). Reference 10 was inserted.

Reviewer C

Comment 1: Page 3, Line 86, no result of water deprivation test was provided. Ref 5 cited here refer to a review paper. Amount of urine, osmolality etc. shall be provided as result, otherwise the diagnosis of CDI is questionable.

Reply 1: Thanks for your valuable suggestion. We added some data on the result of water deprivation test. The urine output decreased from 6.55ml/kg·h to 4.90 ml/kg·h, and urinary osmolality was 298 mOsm/kg with no significant change after desmopressin injection. There was no obvious abnormality on the pituitary magnetic resonance imaging (MRI). Polydipsia and polyuria improved slightly after water restriction. With the above information, the diagnosis was considered to be primary polydipsia. Considering your suggestion, we added some data in our text (see Page 5, lines 90-93). Four months after operation, urine output was 6.35ml/kg·h and urinary osmolality was 301 mOsm/kg， repeated pituitary MRI showed pituitary stalk thickening and cranial computed tomography showed bone destruction, which raised the suspicion of CDI caused by Langerhans cell hyperplasia. Considering your suggestion, we added some data in our text (see Page 6-7, lines 119-125).

Changes in the text: See Page 5, lines 90-93 and Page 6-7, lines 119-125 (marked in red).

Comment 2: what is the incidence of aymptomatic hydronephrosis by newborn and what is the incidence of central diabetes insipidus, both acquired and

inherited? It would be welcome if you proposal could be based on the incidence of disorders, which one is more often, which one is rare. For instance, a considerable idea could be - for newborns with asymptomatic hydronephrosis, special attention shall be draw to rule out co-exisitence of other nephrologic disorders.

Reply 2: Thanks for your valuable suggestion. The incidence of asymptomatic hydronephrosis in newborn is 0.5% to 1%. The incidence of central diabetes insipidus is 3–4 patients per 100,000, among which 6% is inherited. As asymptomatic hydronephrosis is more common, we should pay special attention when it is accompanied with DI, or other nephrologic disorders and symptoms (increased water intake, strenuous exercise or urinary retention). We have modified this part in our text according to your suggestion (see Page 10, lines 190-194). When patients have asymptomatic hydronephrosis, we should always look for concurrent nephrologic disorders. For example, the co-existence of vesicoureteral reflux was found in 25% of newborn with asymptomatic hydronephrosis and it can lead to kidney damage with scar formation and decrease of the renal function. Therefore, we should pay more attention if patients have symptoms, like fever, turbid urine or their ultrasound shows ureteral dilatation. Further examinations, such as urine analysis and VCUG etc. should be obtained to rule out the co-existence of VUR. We have modified this part in our text according to your suggestion (see Page 10-11, lines 208-215).

Changes in the text: See Page 10-11, lines 190-194 and 208-215 (marked in red). Reference 19, 20, 21 were inserted.