Resumen.—El síndrome de Joubert es un trastorno autosómico recesivo severo que se caracteriza por hipotonía, patrón respiratorio alterado y agenesia del vermis cerebelar. El síndrome de Joubert tipo B es un trastorno del desarrollo del nefronoptisis complejo con múltiples alteraciones orgánicas. Aunque es un síndrome raro, desde su primera descripción por Joubert et al. en 1969, hay varios casos que evidencian la importancia de las alteraciones cromosómicas relacionadas con este síndrome. En este trabajo reportamos dos pacientes con síndrome de Joubert en quienes se ha demostrado, mediante ultrasonografía, afectación renal como trastornos quísticos renales que resaltaron la importancia de su diagnóstico y evaluación. La gammagrafía renal con el 

**PALABRAS CLAVE:** síndrome de Joubert, gammagrafía renal, 

**INTRODUCCIÓN**

Renal cystic disease is sometimes associated with abnormalities of the central nervous system like in diseases such as Meckel syndrome and Zellweger syndrome. Joubert syndrome is a rare autosomal recessive disorder whose main clinical signs are hypotonía, ataxia, mental retardation, abnormal eye movements and respiratory pattern. Hypoplasia or absence of cerebellar vermis and incomplete fusion of the halves of the vermis are the most characteristic imaging features. Renal involvement as nephronophtisis (NPH) which takes this syndrome to another type, type B, and adds different clinical features may also be present as medullary cysts.

Joubert syndrome type B is a developmental disorder of the nephronophtisis complex with multiple organ involvement including the renal cystic disorder-NPH, coloboma of the eye, renal dystrophy, aplasia of cerebellar vermis and psychomotor retardation.

Renal cortical scintigraphy with 

**KEY WORDS:** Joubert syndrome, renal scintigraphy, 

**EL PAPEL DE 

**99mTc DMSA GAMMAGRAFÍA RENAL EN EL SÍNDROME DE JOUBERT**

**RESUMEN.—**El síndrome de Joubert es un trastorno autosómico recesivo que se caracteriza por hipotonía, retinopatía, desarrollo atáxico, mental retardation, abnormal eye movements and respiratory pattern. Hipoplasia o ausencia de vermis cerebelar y fusión incompleta de las mitades del vermis son los hallazgos más característicos en la imagen. La participación renal en este síndrome como nefronophtisis (NPH) lo lleva a otro tipo, tipo B, y adquiere otras características clínicas que pueden estar presentes como quistes medulares.

Joubert syndrome type B es un trastorno de desarrollo del nefronophtisis complejo con múltiples alteraciones orgánicas incluyendo la afectación renal-NPH, coloboma del ojo, disfunción renal, aplasia del vermis cerebelar y retardo psicomotor.

**RESUMEN.—**El síndrome de Joubert es un trastorno recesivo autosómico severo que se caracteriza por hipotonía, desarrollo atáxico, mental retardation, abnormal eye movements and respiratory pattern. Hipoplasia o ausencia de vermis cerebelar y fusión incompleta de las mitades del vermis son los hallazgos más característicos en la imagen. La participación renal en este síndrome como nefronophtisis (NPH) lo lleva a otro tipo, tipo B, y adquiere otras características clínicas que pueden estar presentes como quistes medulares.

**RESUMEN.—**El síndrome de Joubert es un trastorno recesivo autosómico severo que se caracteriza por hipotonía, desarrollo atáxico, mental retardation, abnormal eye movements and respiratory pattern. Hipoplasia o ausencia de vermis cerebelar y fusión incompleta de las mitades del vermis son los hallazgos más característicos en la imagen. La participación renal en este síndrome como nefronophtisis (NPH) lo lleva a otro tipo, tipo B, y adquiere otras características clínicas que pueden estar presentes como quistes medulares.
Here we present 2 patients who were diagnosed as Joubert syndrome and whose renal disorder were shown by ultrasonography (USG) later. $^{99m}$Tc-DMSA renal imaging showed bilaterally decreased uptake of the radiopharmaceutical due to the impaired renal function in each case. Joubert syndrome with developmental disorder of the NPH and evaluation of the kidneys with $^{99m}$Tc-DMSA in these cases are discussed.

**CLINICAL CASES**

**Case 1**

A 4 year-old girl with the diagnosis of Joubert syndrome was referred to our department for renal cortical scintigraphy. She was the first child of a family in which the parents were relatives. She began to experience chronic vomiting since her birth and gastroesophageal reflux scintigraphy revealed high grade reflux. Medical treatment was not successful and gastrostomy was placed at the age of 4 years. She also underwent hospitalizations because of fever and weight loss when she was 1-year-old and pulmonary infection at 2-year old age. She suffered from anemia and her present hemoglobin level was 6.3 g/dl. Kidney function deteriorated over the years which is reflected by blood urea and creatinine levels and shown in table 1. She was diagnosed as Joubert syndrome with hypoplasia of cerebellar vermis, perinatal hypoxia, impaired psychomotor development and abnormal eye movements at the age of 2 years. Since 1999, she has been followed by SG examinations with 6 months intervals and serial investigations showed bilateral medullary cysts (fig. 1A) and loss of corticomedullary differentiation (fig. 1B).

For renal cortical scintigraphy $^{99m}$Tc-DMSA (Mallinckrodt Medical B.V., Petten, Holland) was used. Planar images from the posterior and posterior oblique projections were obtained with a single head-ed gamma camera (ADAC, Cirrus) equipped with a low energy high resolution collimator. Four hours after the injection of 48 MBq (1.3 mCi) $^{99m}$Tc-DMSA, scintigraphic image showed diffusely bilateral decreased DMSA uptake in kidneys and visualization of bladder. It also displayed the cysts (fig. 2). During the time of scintigraphy there was no evidence of another pathology such as a recent urinary tract infection or drug interference which might also cause decreased radiopharmaceutical uptake. The findings were consistent with the involvement of kidneys in Joubert syndrome.

### Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Age (year)</th>
<th>Serum creatinine (0-1.13 mg/dl)</th>
<th>Serum urea (5-18 mg/dl)</th>
<th>Serum Hgb (12-18 g/dl)</th>
</tr>
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<tbody>
<tr>
<td>1999</td>
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<td>0.57</td>
<td>17</td>
<td>10.9</td>
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<tr>
<td>2000</td>
<td>2</td>
<td>0.9</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>2001</td>
<td>3</td>
<td>1.12</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>2002</td>
<td>4</td>
<td>3.2</td>
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<td>8.3</td>
</tr>
<tr>
<td>2003</td>
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<td>3.85</td>
<td>58</td>
<td>6.9</td>
</tr>
<tr>
<td>2004</td>
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</tr>
<tr>
<td>2005</td>
<td>7</td>
<td>4.35</td>
<td>26</td>
<td>13</td>
</tr>
</tbody>
</table>

Hgb: hemoglobin.

**Fig. 1.**—Renal ultrasonography shows (A) medullary cysts (arrows) and (B): loss of corticomedullary differentiation.
Case 2

A 6-year-old girl with the diagnosis of Joubert syndrome underwent renal cortical scintigraphy. After birth, she did not have any problems but she had the first experience of apnea after a vaccinating procedure at the age of 4 months. She had nystagmus with moving and searching eye movements and then she presented with polyuria and polydipsia at the age of 1 year. She was hospitalized for high levels of urea for several times which is shown in table 2 and was evaluated by SG examinations. The only abnormality established with USG was corticomedullary cysts.

In DMSA renal scintigraphy, after the injection of 59.2 MBq (1.6 mCi) $^{99m}$Tc-DMSA, bilateral decreased renal DMSA uptake in kidneys (k) and visualization of bladder (b). It also displays the cysts (arrow). (fig. 3). All these findings indicated the impairment of renal tubular function due to Joubert syndrome in the patient.

DISCUSSION

Familial juvenile NPH is a tubulointerstitial disease with development of cysts at the corticomedullary junction of the kidneys and one of the causes of end stage renal disease among children$^7$. It can be presented with polyuria and polydipsia at the age of 1 year. She was hospitalized for high levels of urea for several times which is shown in table 2 and was evaluated by SG examinations. The only abnormality established with USG was corticomedullary cysts.

In DMSA renal scintigraphy, after the injection of 59.2 MBq (1.6 mCi) $^{99m}$Tc-DMSA, bilateral decreased renal DMSA uptake in the kidneys, visualization of bladder and increased background activity were depicted (fig. 3). All these findings indicated the impairment of renal tubular function due to Joubert syndrome in the patient.

Table 2

LABORATORY RESULTS OF CASE 2 OVER YEARS (NORMAL RANGES IN PARENTHESIS)

<table>
<thead>
<tr>
<th>Year</th>
<th>Age (year)</th>
<th>Serum creatinine (0-1.13 mg/dl)</th>
<th>Serum urea (5-18 mg/dl)</th>
<th>Serum Hgb (12-18 g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>3</td>
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<tr>
<td>01.2001</td>
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<td>0.6</td>
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<tr>
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<td>02.2002</td>
<td>6</td>
<td>0.72</td>
<td>20</td>
<td>9.2</td>
</tr>
<tr>
<td>09.2002</td>
<td>6</td>
<td>0.67</td>
<td>23</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Hgb: hemoglobin.
a solitary abnormality and can be a component of Joubert syndrome which is a developmental disorder with multiple organ involvement. In this situation Joubert syndrome type B is considered and this renal cystic disorder alters the clinical presentation. In most cases, progressive renal failure comes along with around puberty and in some patients development of renal failure can not be detected until an advanced stage.

In NPH, USG shows medullary cysts and loss of corticomedullary differentiation. Medullary cysts are highly suggestive of NPH in children with renal failure but they are usually seen in patients with advanced disease. Sometimes cysts can not be observed in patients even in advanced stage and the only sign can be the loss of corticomedullary differentiation.

\(^{99m}\)Tc-DMSA is a highly sensitive tracer for detecting functioning renal cortical tissue and there have been several reports about its utility in different forms of parenchymal and tubulointerstitial diseases. Its usage in detecting renal parenchymal scars and pyelonephritis is the result of its capability of the localization of the radiopharmaceutical in the functioning renal tubules. Its uptake is from peritubular capillaries and when there is lack of functioning renal tubular mass, \(^{99m}\)Tc-DMSA uptake decreases and this can be evaluated by either visually or quantitatively.

In 1991 Quinn et al. have reported a patient with tubulointerstitial disease whose \(^{99m}\)Tc-DMSA renal scan showed poor uptake of the radiopharmaceutical in spite of near normal kidney functions with \(^{99m}\)Tc-DTPA (diethylene triamine pentaacetic acid). They suggested that \(^{99m}\)Tc-DMSA uptake was an index of functioning tubular mass rather than global renal function.

In 1996 Hecht et al. reported 4 cases with NPH who had very poor renal uptake of \(^{99m}\)Tc-DMSA. In that study it has been concluded that the specific tubular function defect in NPH could be the cause of the decreased uptake of \(^{99m}\)Tc-DMSA. Although failure of the binding of the isotope within the cell (biochemical defect) as a cause was not proved, a low radiopharmaceutical uptake together with a normal background activity suggest this mechanism as the cause of the poor visualization of kidneys.

In our cases, renal involvement of Joubert syndrome was clearly diagnosed with bilaterally decreased uptake of \(^{99m}\)Tc-DMSA in the kidneys in renal cortical scintigraphy and also with USG (medullary cysts and loss of corticomedullary differentiation). Visual demonstration of poor radiopharmaceutical uptake, increased background activity and bladder visualization suggest that there is a possible tubular function defect in NPH in Joubert Syndrome and this is the cause of the failure in the uptake of the radioisotope by the tubule.

The histopathological background of NPH is diffuse tubulointerstitial changes. Thickening of the tubular basement membrane (TBM) involves both the proximal and distal tubules and the TBM is lamellated. Dilated tubules are present and surrounded by fibrosis and nonspecific inflammatory cell infiltration. Atrophic tubules may be present. Glomeruli are often normal, although some of them may be completely sclerosed and others may show periglomerular fibrosis. Decreased \(^{99m}\)Tc-DMSA uptake in the kidneys of our patients with Joubert syndrome with NPH might be due to the failure of the uptake by the tubule or defective binding of the isotope within the tubule cell.
and consequently there is $^{99m}$Tc-DMSA leakage in the urine and high background activity. Bladder activity supports this hypothesis (figs. 2 and 3).

Whether the mechanism of the poor renal uptake of $^{99m}$Tc-DMSA is by the tubule or within the cell, NPH causes poor uptake of $^{99m}$Tc-DMSA. $^{99m}$Tc-DMSA uptake is an index of functioning tubular mass and correlates with predominant tubulointerstitial disease. There have been no scintigraphic report about the role of scintigraphy in Joubert syndrome. It is a rare syndrome but can be associated with NPH. Renal involvement changes the nature of Joubert syndrome and also it can develop over the years so it must be diagnosed as early as possible. USG is useful in evaluating medulla and corticomedullary junction about the presence of cysts but this is solely not enough when the function is being investigated. A tubular agent which shows the functioning tubular mass like $^{99m}$Tc-DMSA can shed light into the presence of a functional abnormality. $^{99m}$Tc-DMSA renal cortical scintigraphy may also have the potential of showing the renal involvement prior to anatomical changes in the kidneys.

In conclusion, the presence of renal impairment may change its nature or develop over the years and should be both recognized as early as possible and followed up carefully in Joubert syndrome with NPH. $^{99m}$Tc-DMSA renal cortical scintigraphy can be useful in evaluating the function of the kidneys and give complementary information with SG in this respect.

REFERENCES