

Congenital anomalies of the kidney and the urinary tract in Down syndrome children

Anomalías congénitas del riñón y del tracto urinario en niños con síndrome de Down

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Abstract

Congenital anomalies of the kidney and the urinary tract are congenital diseases related to Down syndrome. There are not specific recommendations. A literature review was made using key words through scientific databases (Pubmed, Science Direct, Ovid, Scholar Google, UpToDate). CAKUT in Down syndrome include glomerulonephritis, kidney agenesis, microcysts, ectopic kidneys, hydronephrosis and hydroureter, even posterior urethral valves and anterior urethra obstruction, and hypospadias. It will be feasible thinking about performing kidney and urinary tract ultrasonography in first week of life. Urethrocystography must be done in selected cases. If urinary incontinence exists, patient has a history of urinary tract infections, vesicoureteral reflux has been diagnosed or if a decrease in glomerular filtration rate has been identified, we should check for vesical dysfunction associated to symptoms and urologic evaluation could be needed (uroflowmetry or urodynamics). It might be adequate an annual clinical follow up of kidney function.

Key words: Down syndrome, CAKUT, diagnostic imaging.

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Resumen

Las anomalías del riñón y el tracto urinario hacen parte de las anomalías congénitas relacionadas con el síndrome de Down. No existen recomendaciones específicas. Para el presente estudio, se hizo una revisión por palabras clave en bases de datos (Pubmed, Science Direct, Ovid, Google académico, UpToDate). Se encontró que, en niños con síndrome de Down, las enfermedades congénitas del riñón y el tracto urinario abarcan glomerulonefritis, agenesia renal, microquistes, riñones ectópicos, hidronefrosis, hidrouréter, valvas uretrales posteriores, obstrucción de la uretra anterior e hipospadias. Con respecto a los procesos diagnósticos, sería razonable realizar una ecografía renal durante la primera semana de vida. Adicionalmente, la uretrocistografía sería útil solo en casos seleccionados. Si hay un historial de incontinencia urinaria o de infecciones urinarias de repetición; o se detecta un reflujo vesicoureteral, o caída de la tasa de filtración glomerular estimada, debería considerarse la existencia de una disfunción vesical asociada y podría ser pertinente una evaluación urológica (uroflujometría o urodinamia). Sería recomendable hacer un seguimiento clínico anual de la función renal.

Palabras clave: síndrome de Down, enfermedades congénitas, enfermedades renales, enfermedades urológicas, diagnóstico por imagen.

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Introduction

Down syndrome is the most frequent chromosomopathy, which involves several mechanisms in which there are three copies (trisomy), complete or partial (critical region), of chromosome 21. Its incidence is 1.0-1.1 per every 1,000 live births, according to the WHO. In Latin America, it is 1.88; and in South America, 2.9 per every 1,000 live births.² In Colombia, the available data point to an incidence of 0.5- 1.5 per every 1,000 live births.^{3,4}

Congenital anomalies of the kidney and urinary tract (CAKUT) include a varied group of malformations caused by alterations in the renal embryology. Their etiology is multifactorial and they represent between 15 % and 20 % of the anomalies documented prenatally, with a rate of 0.3 – 1.3 per every 1,000 newborns. They are the leading cause of kidney failure in childhood⁵ and their estimated prevalence in Colombia is 0.2%-0.4%.⁶

The pathologies of the CAKUT group are part of the malformations associated with Down syndrome. They have an estimated prevalence of 2.3%-3.2%, which is about five times higher than the one known in children without the chromosomopathy.^{7,8,9} Even more, in the long term, the commitment of the urinary tract can rise up to 27%, including congenital and acquired diseases.¹⁰

These diseases are important, although they are not those which cause the highest morbidity and mortality in the short term (this place is occupied by cardiorespiratory and gastrointestinal pathologies).¹¹ Notwithstanding the foregoing, there are no current recommendations that make them part of the group of pathologies of compulsory surveillance in the global guidelines of Down syndrome.^{12,13} For these reasons, the present document was intended to gather the latest information about the potential benefit of a specific anticipatory management.

Methodology

A review by key words was conducted in the following databases: Pubmed, Science Direct, Ovid, Google Scholar and UpToDate. The following key words were used: Down syndrome and renal disease, Down syndrome and urologic disease, Down syndrome and glomerulonephritis, Down syndrome and renal failure. Cross references were also used. The search window was restricted to articles available in the last 20 years, which corresponded to book chapters, topic reviews, case reports, case series and cohorts.

Epidemiology

In Down syndrome, the CAKUT group covers glomerulonephritis, renal agenesis, microcysts, ectopic kidneys, abnormalities of the urinary tract with hydronephrosis and hydroureter, posterior urethral valves and obstruction of the anterior urethra, as well as hypospadias.^{7,13,14} Without discriminating by underlying pathology, it is known that up to 4.5% of patients with Down syndrome may suffer from a chronic kidney disease.¹⁵

Glomerular disease usually appears between the second and third decades of life. IgA nephropathy and focal segmental glomerulosclerosis are the most frequent pathologies.^{16,17,18,19} It has been suggested that the immune dysfunction associated with Down syndrome may predispose children to postinfectious glomerulonephritis, but there are few data available.^{16,20,21} There could be a higher frequency of ANCA antibodies-associated glomerulonephritis than in children without the syndrome.^{19,22}

With regard to the cysts, it has been described a substantial increase in the incidence of both micro and macrocysts, but the clinical significance of this difference is unknown.¹³ Autosomal recessive polycystic kidney disease may be more common in children with Down syndrome, due to its gene located on chromosome ^{21,23}

It raises concern that up to 4 % of cases of posterior urethral valves can correspond to children with Down syndrome. This makes us think that obstructive uropathy in this specific population is underestimated, although this difference with obstructive uropathies in general is not clearly observed.^{13,24,25,26,27} It has been reported alteration of the prostatic development with consequences similar to the urethral valves.⁹ In addition, the presence of prune belly phenotypes associated with trisomy 21 is known, even in girls.²⁸

Unilateral renal hypoplasia or agenesis also seem to be more frequent in children with Down syndrome; case that is not seen in hypospadias or epispadias.¹³

On the basis of the foregoing, it is considered that most findings are minor alterations, but they are perceived quite heterogeneously.¹⁵

It is expected that the proportion of chronic kidney disease will increase in the long term, since there is a greater survival of these individuals.²⁹

In relation to the functional commitment, it is known that there could be urodynamic involvement in up to 30% of children³⁰ and in 8.7% of adults with the condition.³¹ Although it is known that children with Down syndrome take longer to develop sphincter control (4-5 years), that girls tend to be more continent and that there may be incontinence to a greater extent (12% -16%), it is still not clear how much the urodynamic alterations could contribute to the problem.^{30,32,33}

In its most severe form, the Hinman-Allen syndrome (non-neurogenic bladder dysfunction), there is an obstruction caused by active contractions of the external bladder sphincter during emptying. It can lead to renal failure and it may require derivative bladder surgery.³⁴

There are also reports of hypercalciuria, cystinuria and uricosuria in children with Down syndrome.^{23,15,20} It has even been reported a new mutation associated with congenital nephrogenic diabetes insipidus.³⁵ Finally, it is known that there

is a lower risk of urologic neoplastic pathology in people with Down syndrome.³⁶

Diagnosis

Antenatally, it has been suggested a possible benefit of performing an invasive chromosomal analysis whenever obstructive fetal uropathy is detected.^{9,23} However, it seems better to use ultrasound follow up,³⁷ along with the non-invasive screening test.³⁵

After birth, it would be favorable that all patients with Down syndrome clinically and/or genetically confirmed undergo a renal ultrasound during the first week of life, given the possibility of renal hypoplasia/agenesis or obstructive uropathy, especially when an adequate prenatal ultrasound was not performed.^{38,39} This procedure would also be recommendable whenever functional problems are found.³⁰ Even, for this reason, it is proposed to carry it out annually.^{14,33} A voiding urethrocytography should be the examination complementary to the ultrasound (since there are more structural than functional alterations), following the general indications of the test.³⁹

If there are symptoms of urinary incontinence or recurrent urinary tract infections, or vesicoureteral reflux (VUR) or a decrease in the estimated glomerular filtration rate is detected, the existence of an associated vesical dysfunction should be considered and an urologic evaluation (uroflowmetry or urodynamics) could be relevant.^{33,40} It has been proposed to have in the requirements a low threshold to benefit more children with these tests.¹⁴

The performance of an urinalysis, and the measurement of the excreted fractions of sodium and potassium, the tubular reabsorption of phosphates, the urinary excretion of calcium, magnesium, uric acid, and the clearance of creatinine and proteinuria, would be subject to the ultrasound findings or to the appearance of clinical symptoms of kidney disease according to the specific guidelines for each pathology.¹⁵

It is known that people with Down syndrome suffer more frequently from hyperuricemia and

have a higher risk of suffering from gout. Although there is no clarity about the moment when the measurement should be carried out, it may be appropriate to establish uric acid levels if renal failure is diagnosed.²⁰

Given the varied etiology of glomerulonephritis in Down syndrome, it is not easy to predict its course. However, it can lead to end stage renal failure with replacement therapy and even to renal transplantation. Therefore, renal biopsy is necessary whenever is considered that patients exhibit these pathologies.¹⁶

It is known that the creatinuria and the urine density are lower in children with Down syndrome, with respect to children without the condition. This finding is more noticeable as age increases and could be related to the increased oxidative stress and premature aging observed in these individuals, especially when they are hypothyroid. A specific usefulness of these biomarkers has not been established, but it is an element that suggests the need to do periodic follow-up of the renal function in patients with Down syndrome.^{15,41,42,43,44} In the absence of specific recommendations, it would seem reasonable to make an annual evaluation, as in other pathologies.

Therapeutic approach

The management of each pathology is based on its usual indications. In surgical cases, there will be conditioning factors, according to the existing comorbidities, basically cardiovascular and respiratory.

A basic measure of childcare for children with Down syndrome is to establish continence training. A simple method that can be discussed with the parents is available online.⁴⁵

It should be mentioned that clean bladder catheterization for renal preservation and continence can be performed in people with Down syndrome,

regardless of their cognitive commitment.³⁴ In cases with established renal disease, the annual clinical-ultrasound follow-up has already been mentioned. Additional tests would be done based on this evaluation.

As far as possible, renal replacement therapy should be offered to children who may require it (usually they will be adolescents or older). In these cases, the use of hemodialysis seems to be better, due to the cognitive disability of the patients.⁴⁶ However, if the family environment is adequate, the use of peritoneal dialysis is possible.^{13,20,47,48,49,50} In cases in which is feasible and beneficial, renal transplantation should be offered with the same consideration of the family environment.^{51,52} The rejection rate is similar than in other conditions.^{20,53,54}

Conflict of interest

The author makes explicit that he is part of the Down Syndrome Research Group of Santander, which has no direct affiliation with any other entity and does not have any other purpose apart from academic, for the benefit of children with Down syndrome. He declares that no remuneration of any type was received for the development of this manuscript and that no material compensation is received for the connection with the aforementioned research group.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

The author declares that has followed the protocols of their workplace on the publication of patient data.

Right to privacy and informed consent

The authors state that patient data do not appear in this article.

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