Two siblings with acute lymphoblastic leukaemia: Chance or genetics?

Dos hermanos con leucemia linfoblástica aguda: ¿casualidad o herencia?

Dear Editor:

Acute lymphoblastic leukaemia (ALL) is the most frequent childhood cancer and accounts for 80% of cases of acute leukaemia. Its underlying mechanisms are largely unknown. There is growing evidence of the role of genetic factors in its aetiology. This statement is based on the following: (1) there is a strong association between ALL and some chromosomal translocations; (2) the incidence of acute leukaemia is greater in relatives of patients with acute leukaemia, and (3) there is a higher incidence of leukaemia in individuals with certain genetic syndromes (Down syndrome, Klinefelter syndrome, neurofibromatosis, Shwachman syndrome, etc.).

In recent years, genetic mutations associated with an increased risk of ALL have been reported, in spite of which its heritability remains uncertain. We present a case of ALL in a sibling of a patient that had received a diagnosis of ALL 4 years earlier.

The patient was a boy aged 18 months brought to the emergency department with fever of up to 39°C lasting 2 days and associated with cold symptoms and breathing difficulties. There had been no complications during pregnancy, delivery or the neonatal period. The boy had received vaccinations conforming to the official schedule. There were no other medical or surgical diseases. The complete blood count revealed pancytopenia. A bone marrow sample was obtained 48h after admission whose analysis revealed infiltration with 60% of blast cells and markers compatible with common ALL (B-cell precursor). The relevant family history included an older brother aged 6 years with B-cell precursor ALL diagnosed 4 years earlier that had completed treatment 2 years after the diagnosis. The father had insulin-dependent diabetes mellitus since age 25 years, the mother was healthy, and a paternal aunt had died of cancer at age 40 years.

The 2 siblings were treated according to the PETHEMA BR protocol and responded well to chemotherapy. Both are in full remission at present, 6 and 10 years after diagnosis, respectively.

Most cases of ALL in children are sporadic, and ALL is not considered an inherited disease. Direct evidence of a genetic heritable predisposition to ALL due to certain genetic syndromes, such as Bloom syndrome, neurofibromatosis, ataxia-telangiectasia and trisomy 21 is only found in a small percentage of ALL cases (<5%). The genetic basis of the heritable susceptibility to ALL outside these syndromes has not been elucidated. However, there have been advances on this matter in recent years: genomic studies have found that somatic variants of ARDSB, IKZF1 and CDKN2A are associated with an increased risk of ALL (odds ratio, 1.3–1.9). Other rare germine mutations in PAX5, ETV6 and especially p53 may also predispose to leukaemia.

Despite all these findings, there is no sufficient evidence to prove a familial risk of ALL in children, which may be due, in part, to the low incidence of the disease. A Scandinavian study that included 3,994 patients with ALL identified 36 cases of ALL in siblings: 10 cases in singleton siblings and 26 in twins. The study showed that compared to the general population, twins of children with ALL had an increased risk of developing leukaemia (standardised incidence ratio [SIR], 163; 95% CI, 70–320), while the increase in risk in singleton siblings was small (SIR, 3; 95% CI, 2–6). It is believed that the high risk found in twins results from sharing the prenatal blood circulation. The increased risk in singleton siblings is not associated with the aforementioned genomic findings, so the authors suggested that other germine mutations or polymorphisms yet unknown may underlie this familial effect. To date, this is the first study in the literature that attributes an increased risk of developing ALL in siblings of patients with the disease.

In the case of our patient, in whom none of the findings suggested the presence of a genetic syndrome associated with an increased predisposition for ALL, and based on the data currently available in the literature, we did not have sufficient evidence to establish whether this familial aggregation was hereditary in nature. On the other hand, since the incidence of ALL is low in the general population and the mild increase in the relative risk of siblings of patients with ALL does not result in a high probability of developing leukaemia, we do not recommend routine screening of siblings of patients with leukaemia.

It is important that research on the genetic basis of ALL continues, not only to establish its heritability, but also to learn its potential impact on prognosis and treatment.

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Early kidney damage in patients born with unilateral renal agenesis

Daño renal precoz en pacientes nacidos con agenesia renal unilateral

To the Editor:

Unilateral renal agenesis, or solitary kidney, is a common disease (1/720 births) with a predominance of male patients. It affects the left kidney most frequently. Its aetiology and pathogenesis are unknown, with the literature describing possible genetic and environmental mechanisms.\(^1\) Given its frequent association with other malformations, some authors hypothesise that it may be part of a syndrome.\(^1,2\) The diagnosis is made by ultrasonography, usually before birth. Performance of a nuclear medicine assessment is recommended to rule out nephrourologic comorbidities. These patients are at higher risk of developing proteinuria, chronic kidney disease (CKD) and/or high blood pressure, and unilateral renal agenesis is a frequent cause of CKD in children aged less than 5 years.\(^3,4\) In this article, we describe our experience with this disease.

We conducted a retrospective, observational and descriptive study by collecting data from the health records of children born with unilateral renal agenesis in our hospital between 2008 and 2015. We found records for 21 patients (57% male) with a mean age of 3.8 years for the period under study. Forty-five percent of the patients had a prenatal diagnosis of unilateral renal agenesis, which was confirmed postnatally by renal ultrasound in all. Of the remaining 55%

that received the diagnosis after birth, 66% had some type of malformation at birth (most frequently gastrointestinal), and underwent a renal ultrasound examination for the purpose of ruling out associated nephrourologic malformations (which were found in 45%, with a predominance of pelvicaliectasis [29%] and vesicoureteral reflux [VUR] [21%]). Other, less frequent reasons that led to diagnosis were oligohydramnios, spina bifida or acute pyelonephritis in the early days of life (11%).

There were more cases of left-sided renal agenesis (65%), and a solitary hypertrophic kidney was detected in 55% of cases. All patients underwent a workup that included measurement of plasma urea and creatinine levels, urinary sediment analysis and calculation of the albumin/creatinine ratio, and the results were normal in all at the time of testing. The evaluation was completed with imaging of the kidney by \(^{99m}\)Tc-mercaptoacetyltriglycine (MAG3) renography in 80% and serial voiding cystourethrography (VCUG) in 30% of patients. Eighty-one percent of patients were followed up in outpatient services (median duration, 3 years; range, 0–7 years), with periodic checkups including measurement of blood pressure, renal ultrasound examination, renal function panel, albumin/creatinine ratio, urinary sediment analysis and calculation of the glomerular filtration rate (GFR) using the Schwartz formula updated in 2009. We found no cases of high blood pressure. Thirty-five percent of patients had at least one episode of acute pyelonephritis that responded well to antibiotic treatment. Fifty percent of these patients had VUR and received prophylactic antibiotic therapy. Three patients (17%) developed early CKD, associated with microalbuminuria in 1 (Table 1). None of the patients needed renal replacement therapy.

One of the salient findings of our study was the high morbidity associated with unilateral renal agenesis, which was consistent with the literature. For instance, Westland et al.\(^5\) analysed 2684 cases of unilateral renal agenesis in children and adults and found high blood pressure, microalbuminuria and chronic kidney disease with a GFR of less than 60 mL/min/1.73 m\(^2\) in 16%, 21% and 10% of

\(^{1}\) Please cite this article as: Castellano-Martinez A, Rodriguez-Gonzalez M, Roldan-Cano V. Daño renal precoz en pacientes nacidos con agenesia renal unilateral. An Pediatr (Barc). 2017;87:171–173.