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Editorial

Kidney-vascular-bone axis in down syndrome

El eje riñón-vaso-hueso en el síndrome de Down

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Introduction

Down syndrome (DS) is the most common chromosomal disorder in live newborns and the leading cause of congenital mental disability in Western countries, with an estimated incidence of 14.5 per 10,000 live births in the United States.[1]

In most cases it is due to a trisomy in chromosome 21, although there are also reported cases with translocations at another level (Robertsonian) or mosaicisms. Currently, the greater availability of prenatal screening protocols has increased gestational diagnosis from 7 to 9 times. It is known that the increase in maternal age at the time of conception is directly related to the increasing incidence of DS; however, the global birth prevalence of DS has remained stable due to a parallel increase in losses due to termination of pregnancy.[2]

There is considerable phenotypic variation among patients, as well as differences in incidence and presentation according to ethnic and geographic origin.[3]

Adults with DS have their own health problems and clinical characteristics, mainly characterized by an early and accelerated aging process, as well as earlier mortality than the rest of the population. In recent decades there has been a considerable and progressive increase in the life expectancy of subjects with DS, currently standing at more than 60 years[4]; this is due to medical advances, such as improvements in cardiac surgery, prevention of infections in childhood, greater access to standard care and more comprehensive psychosocial support.[5]

For the description of the clinical profile of adults with DS, previous approaches have been based on population studies according to death certificates, hospital admission diagnoses or retrospective series. All these studies indicate that adults with DS present unique medical problems that differ from those of the general population, the most frequent being ophthalmological diseases, musculoskeletal disorders and dementia, and also including others such as gastrointestinal manifestations, hearing loss, anomalies hematological such as leukemia, congenital hypothyroidism and hypotonia.

The main causes of early mortality in this population are congenital heart disease, cardiac arrhythmias, pulmonary hypertension, cardioembolic stroke or dementia itself.

The objective of this article is to describe the existing literature and compare this information with our own data (unpublished) from a monographic outpatient clinic of adults with DS. From this clinic, information from a group of 81 subjects with DS has been extracted. This is the group of patients that will be referred throughout this editorial manuscript.

Cardiovascular risk in people with Down syndrome

People with DS have been proposed as a model free of atherosclerosis without having biological explanation for the time being. The relationship between cardiovascular events and factors such as hypertension, dyslipidemia, obesity or diabetes mellitus has been widely demonstrated in the general population. People with DS present generalized obesity and dyslipidemia without that is not translated into an increased cardiovascular risk. In fact, the data from the DS clinic at our center show a 6% prevalence of hypertension (mean systolic

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blood pressure of 114 ± 13.4 and mean diastolic blood pressure of 68 ± 11.4 mmHg). A 19% dyslipidemia and 0% diabetes mellitus, although the body mass index is very high (mean 29.2 ± 6.4 kg/m^2).

This theoretical cardiovascular advantage has its confirmation in the analysis of subclinical parameters of arteriosclerosis. In accordance with the published literature, the data from our center reaffirm the cardiovascular protection of subjects with DS.[6] Thus, the intima-media thickness of people with DS is found to be in our environment at 0.54 ± 0.10 mm in men and 0.52 ± 0.07 mm in women, a pulse wave velocity of 7.1 ± 1.9 m/s in men and 6.5 ± 1.8 m/s in women, parameters similar to those of the healthy population without cardiovascular risk.[7]

Epidemiological studies at the population level have tried to clarify this circumstance and its prognostic impact, mainly cardiovascular. In one of the largest papers published to date, Sobey et al. evaluated two cohorts of hospitalized patients, comparing those with and without DS with a mean follow-up of 17 years.[8] The authors show that patients with DS have an increased risk of stroke with protection against the development of coronary events. However, the group of patients with DS had a significantly higher prevalence of cardioembolic factors (congenital heart disease, arrhythmias, or pulmonary hypertension) but a lower rate of atherosclerotic factors, which obviously makes it difficult to interpret the results.

Although the evidence derived from clinical intervention trials is limited in the field of cardiovascular protection, small studies have been able to demonstrate that increased physical activity in people with DS improves body composition and even cognitive functions, although to date, there is no study that evaluates its impact on cardiovascular events.[9,10]

In the registry of patients with DS in our center we found a high body mass index, but with a body composition (determined by bioimpedance spectroscopic and confirmed with densitometry-DXA) with findings of special interest. It is observed that most of the patients present overhydration (mean excess water of 2.7 ± 1.6 L). In addition, a detailed study of body composition shows a similar percentage of lean mass and fat mass (11.9 ± 7 kg/m^2 and 14.8 ± 3.7 kg/m^2, respectively). Although this situation could be assocated to a better functional and physical capacity, a recent study has been able to show that, unlike the general population, the muscle of people with DS does not generate a cardiorespiratory benefit.[11] The explanation for this phenomenon is based on several points, such as, autonomic dysfunction or mitochondrial alterations typical of DS that prevent an appropriate function of the muscles.[12]

Regarding emergent cardiovascular risk factors, uric acid presents an interesting controversy. People with DS have high levels of uric acid (in our series, 28% have hyperuricemia, with mean uric acid level of 5.9 ± 1.2 mg/dl), but none of the patients analyzed had presented episode of gout and there was no association of this parameter with arterial hypertension or metabolic syndrome. In addition, a protective effect of uric acid on certain dementias has been proposed, especially with Alzheimer's disease, through a modulation of oxidative stress.[13] It should be remembered that people with DS develop dementias more frequently, so the pathophysiological role of uric acid in this population has yet to be established. For all these reasons, despite the fact that classical therapeutic inertia may lead us to treat hyperuricemia, we currently do not have enough evidence to recommend this therapeutic approach in DS.

Kidney disease in Down syndrome

Beyond renal and ureteral malformations, such as pyeloureteral stenosis, vesicoureteral reflux, renal hypoplasia, obstructive uropathy, posterior urethral valves, and some isolated cases of asymptomatic renal pelvic dilatation and left renal ectopia, kidney disease in DS is a great unknown.[14]

The estimation of renal function based on creatinine has obvious drawbacks in the population with Down syndrome. Knowing the unusual body composition of these patients the prevalence of kidney disease may be often underestimated. In a recent study in children, it is shown that the factors that affect creatinine determination should be assessed in the context of DS, since they show large differences with children without DS.[15]

In fact, in our practice the mere fact of adjusting the formula for estimating glomerular filtration rate for body surface area in patients leads to a substantial increase in the prevalence of kidney disease (from 2.7% to 9.8%). The problem probably lies in the use of the creatinine parameter in a population that has a smaller kidney structure and less functioning nephron mass than people without DS.[16] The data obtained from patients in our center show that the kidneys that are reduced in size (mean 9.4 ± 0.9 cm) but with normal echostructure.

Within the alternatives to creatinine, and avoiding the tedious isotopic techniques, we have some markers of interest to estimate renal function. However, in the population with DS, we found only some brief report on the use of cystatin C, which shows a good correlation with creatinine in the population with DS.[16] Interestingly, the data derived from our own experience reveal that the use of cystatin C in this population requires, even more than creatinine, an adaptation. The mean cystatin C in our patients is 1.29 ± 0.18 mg/L, a value that is much higher than normal for the assay (reference of the technique 0.53–0.95 mg/L). Thus, the application of Hoek's formula established an estimated mean glomerular filtration rate of 58 ± 8 ml/min/1.73 m^2.

The information available on urinary data is really scarce due to the difficulty of collecting the urine. In the few published studies, mainly based on the pediatric population, proteinuria is very infrequent, but hyperuricosuria may be observed from early ages.[17] These findings are difficult to interpret as they were obtained in the pediatric population, but they could reflect another element of cardiovascular protection.

Regarding the etiology of renal dysfunction, few specific cases of histological data have been reported due to the technical difficulty involved in performing a renal biopsy.[18] However, it is likely that in the coming years, as a result of these people's access to health care, this type of low-risk interventional procedures will increase and we will have more information. The performance of renal replacement therapy in this popula-

tion group is absolutely exceptional and there are hardly any published cases.[19]

From our point of view, and in the absence of established protocols, we consider that the renal function of people with DS should be established using analytical parameters (creatinine and, if available, cystatin C), but also using imaging tests such as ultrasound. In addition, it seems necessary to consider the need to validate a new specific method for the correct diagnosis of kidney failure in DS, which takes into account the characteristics of this population, such as differences in body composition and its situation of chronic oxidative stress.

Bone mineral metabolism in Down syndrome

To fully understand organ function in DS, we must delve into bone-mineral metabolism and its interrelation in the bone-vessel-kidney axis.

Although with some controversy, the bone mineral density of subjects with DS is decreased, which is relevant given the predisposition to present fractures.[20] Numerous factors have been associated with this situation, which have become more evident with the increased survival of this population. Such factors are, for example, a sedentary lifestyle, muscular hypotonia or low exposure to vitamin D. In our group, we have performed densitometry in 14 patients, in which only 29% showed absence of alterations and up to 36% severe osteoporosis (taking into account the T-score).

The measurement of bone mineral density, although it has been shown to be a good predictor of fractures, has certain limitations, which have been improved with the use of other techniques, such as the bone trabecular index, the volumetric adjustment of mineral density or even the use of high-resolution computed tomography.[21] It should be remembered that bone formation occurs early in life. This temporal aspect has been valued by some authors, showing that subjects with DS present an early and less pronounced bone mass peak as compared with the general population.[22]

. The analytical parameters and their association with bone mineralization are mainly based on the action of vitamin D; which is secondary, among other things, to their psychosocial situation, people with DS more frequently present decreased levels of vitamin D[23] In the only clinical trial published to date, based on 23 institutionalized subjects with DS, administration of 1 g of calcium and 800 IU of vitamin D once daily produced an improvement in biomarkers of bone formation without changes in calcium and serum phosphorus.[24] Although these results are not enough to recommend universal vitamin D and calcium supplementation, data on real life show that it is a very common practice.[4,25] In fact, in an elegant clinical trial that included 48 children with DS randomized into four groups to receive calcium with or without physical exercise (45 min, three times a week), physical exercise itself was shown to increase bone density superior to calcium administration, which casts doubt on the role of its isolated supplementation.[26]

The data from our clinic is superimposable to those of the general population (calcium 9.3 ± 0.4 mg/dl, phosphorus 3.5 ± 2.3 mg/dl, vitamin D 31 ± 17 ng/ml and intact parathyroid hormone 39 ± 16 pg/ml). However, these data must be contextualized in the usual clinical practice of the monographic clinic in which many patients (>50%) receive vitamin D supplements (with or without calcium supplements).

Therefore, with the available evidence, screening for osteoporosis and osteopenia in people with DS seems reasonable, trying to avoid or mitigate modifiable factors. The series of analytical measurements of calcium, phosphorus, vitamin D and PTH must be individualized according to the density of the bone mass of each person.

Conclusions

DS is a model free of atherosclerosis through mechanisms that are not explained at the present time. According to the existing evidence, renal function in DS requires adaptation of the usual measurement methods and imaging tests must be considered in its assessment. People with DS have a high predisposition to osteoporosis with the consequent risk of fractures. There is currently a general lack of evidence on the clinical management of people with DS, which opens new avenues for its deepening from a scientific point of view.

Conflicts of interest

None.

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