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Hyperuricemia in Down syndrome children and adolescents

Hiperuricemia em crianças e adolescentes com síndrome de Down

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ABSTRACT

Introduction: Patients with Down syndrome (DS) seem to have higher rates of hyperuricemia, although there are very few studies that address this issue. High levels of uric acid (UA) are an independent risk factor for atherosclerotic heart disease. **Objective:** To study the prevalence of hyperuricemia in DS children and its distribution according to age. **Methods:** Retrospective study of 139 DS patients aged 1-14 years for serum UA values considering the normal cut-off values for age. **Results:** Among the 139 included patients, 70 (50.4%) were males, 69 (49.6%) were females, and the mean age was 5.31 ± 3.49 years (range 1-14 years). In this sample, 39 (28.1%) had serum UA levels above the normal value. We did not find differences in the serum UA according to gender, except in patients in the range of 13-15 years, where males had mean UA levels of 5.75 ± 1.37 mg/dl; and females, of 8.02 ± 0.77 mg/dl ($p = 0.02$). **Conclusion:** We found a high rate of hyperuricemia in children with DS that equally affects both genders, except in the age range of 13-15 years, in which it was more common among females.

Key words: uric acid; Down syndrome; children.

RESUMO

Introdução: *Pacientes com síndrome de Down (SD) parecem ter maior hiperuricemia, embora existam poucos estudos que abordem essa questão. Níveis altos de ácido úrico (AU) são um fator de risco independente para doença cardíaca aterosclerótica.* ***Objetivo:*** *Estudar a prevalência de hiperuricemia em crianças e adolescentes com SD e sua distribuição de acordo com a idade.* ***Métodos:*** *Estudo retrospectivo de 139 pacientes com SD entre 1 e 14 anos de idade, para valores de AU, considerando os valores de corte normais para a idade.* ***Resultados:*** *Dos 139 pacientes incluídos, 70 (50,4%) eram do sexo masculino e 69 (49,6%), do feminino; a média de idade foi de 5,31 ± 3,49 anos (variação de 1-14 anos). Nesta amostra, 39 (28,1%) apresentaram níveis séricos de AU acima do valor normal. Não foram encontradas diferenças na concentração sérica de AU segundo o sexo, exceto em pacientes na faixa de 13 a 15 anos, na qual os meninos apresentaram níveis médios de AU de 5,75 ± 1,37 mg/dl e as meninas, de 8,02 ± 0,77 mg/dl (*p *= 0,02).* ***Conclusão:*** *Encontramos alta taxa de hiperuricemia em crianças com SD, que afeta igualmente ambos os sexos, exceto na faixa entre 13 e 15 anos de idade, em que foi mais comum no sexo feminino.*

Unitermos: *ácido úrico; síndrome de Down; crianças.*

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RESUMEN

Introducción: *Pacientes con síndrome de Down (SD) perecen tener mayor grado de hiperuricemia, aunque hay pocos estudios que traten esa cuestión. Niveles elevados de ácido úrico (AU) son un factor de riesgo independiente para enfermedad cardiovascular aterosclerótica.* ***Objetivo:*** *Estudiar la prevalencia de hiperuricemia en niños y adolescentes con SD y su distribución de acuerdo a la edad.* ***Métodos:*** *Estudio retrospectivo de 139 pacientes con SD y edades entre 1 y 14 años para valores de AU, considerando los puntos de corte normales según edad.* ***Resultados:*** *En los 139 pacientes incluidos, 70 (50,4%) eran del sexo masculino y 69 (49,6%) del femenino; la edad media fue 5,31 ± 3,49 años (rango: 1-14 años). En esta muestra, 39 (28,1%) presentaron niveles séricos de AU por encima de lo normal. No fueron encontradas diferencias en la concentración sérica de AU por sexo, salvo en pacientes en la franja entre 13 y 15 años, en la que los niños presentaron niveles medios de AU de 5,75 ± 1,37 mg/dl y las niñas, de 8,02 ± 0,77 mg/dl (*p = *0,02).* ***Conclusión:*** *Encontramos alto índice de hiperuricemia en niños con SD, que afecta igualmente a ambos sexos, salvo en la franja etaria entre 13 y 15 años, en la que fue más común en el sexo femenino.*

Palabras clave: *ácido úrico; síndrome de Down; niños.*

INTRODUCTION

The most common chromosomal abnormality in newborns with intellectual disabilities is the Down syndrome (DS), with a worldwide prevalence of about 10 per 10,000 newborns[1-3]. DS is associated with a wide variety of medical problems, ranging from congenital heart disease to dementia or recurrent respiratory infections[1-3]. Some authors have found that patients with DS may have hyperuricemia, although the reasons for this finding were not completely understood[4-6].

Uric acid (UA) is generated by purine catabolism[6]. The majority of mammals convert UA to allantoin by uricase, which is not present in primates[6]. High UA levels increase the body's ability to retain sodium and raise blood pressure. This was considered beneficial in situations of food shortage[6, 7]. However, with the eating habits of the modern diet, rich in salt and UA precursors such as fructose, it has been observed that high levels of UA are associated with hypertension, coronary artery disease, peripheral vascular disease, renal failure and strokes[8, 9].

Recent data indicates that adults with DS are at an increased risk for cardiovascular disease and this has contributed significantly to their morbidity and mortality[10]. Taking into account that high UA is an independent risk factor for atherosclerotic heart disease[11], this may become an issue as DS patients survival is increasing with better care[12].

In the present study, we aimed to assess the prevalence of asymptomatic hyperuricemia in children and adolescents with DS.

METHODS

This is a retrospective study approved by the local Research Ethics Committee. Records of DS patients from a single specialized outpatient clinic, treated from January 2010 to December 2014, were reviewed for uric acid values. To be included, the patients should have DS diagnosis confirmed through karyotype and be aged 1-15 years. Among 281 analyzed records, 142 were excluded for not having UA measurements and four for being out of the pre-established age. Therefore, the study sample was made up of 139 individuals. In addition, all the included patients were evaluated for renal lithiasis, by means of the results of the complete abdominal ultrasound, performed as a protocol in children with DS, checking for the presence of congenital alterations and its possible complications. The adopted UA cut-off levels were 4.8 mg/dl for 1-3 years of age, 5.5 mg/dl for 4-6 years, 5.9 mg/dl for 7-9 years, 6.1 mg/dl for 10-12 years and 7 mg/dl (male) and 6.2 mg/dl (female) for 13-15 years[12]. UA levels were determined in peripheral venous blood samples by a peroxidase-uricase method. The measurements were carried out by an automatic sample analyzer.

Data was collected in frequency and contingency tables. Data distribution was tested by using the Kolmogorov Smirnov test. Comparison studies were based on Fisher and chi-squared tests for nominal data, and unpaired *t*-test for numerical data. The level of significance was set at 5%.

RESULTS

Among the 139 included patients, 70 (50.4%) were males, 69 (49.6%) were females, and the mean age was 5.31 ± 3.49 years (range 1-14 years). In this sample, 39 (28.1%) had serum UA concentration above the normal value. The mean UA values, as well as the number of hyperuricemic patients according to the age group, are seen in **Table 1**.

The comparison of UA values and the number of hyperuricemic patients according to gender in each age group are seen in **Table 2**.

No ultrasound examination showed nephrolithiasis, although 16/139 (11.9%) had pyelocaliceal dilatation. Eight (5.8%) children had gallstones (five boys and three girls, aged between 3-11 years old).

DISCUSSION

The results of the present study showed high prevalence of hyperuricemia in DS patients, encompassing almost one third of the whole sample. Our results are very similar to those of Kashima *et al*. (2014)[12], who found a prevalence of hyperuricemia in 32.7% of their 52 pediatric patients with DS against 4.5% in the control group. There are several hypotheses to explain this finding. They include decreased basal metabolic rate, reduced physical activity and unbalanced diet with consequent obesity[12]. Another is that UA is increased as a compensatory anti-oxidant response to augmented production of reactive oxygen species (ROS) in these patients[13, 14]. UA has a powerful antioxidant activity, which is responsible for about 60% of ROS elimination[15]. The gene of superoxide dismutase 1 (SOD1) is located in a region of the distal part of chromosome 21 (21q22 band), which is tripled and known as the critical region of DS. Increased SOD1 results in hydrogen peroxide produced in excess, what is able to generate deleterious ROS[13].

We did not find gender differences either in the number of hyperuricemic patients or between the mean serum UA levels, except for those aged 13-15 years. Interestingly, we found that females in this age range had higher UA than males. This was not expected, as the ones studied were normally menstruating females, and estrogens are considered to have a uricosuric effect[16]. However, we do not have data on the menstrual status of these patients. It is also very important to note that the sample in this age range was quite small and may not have allowed a correct observation.

TABLE 1 – Serum UA mean values and prevalence of hyperuricemia according to age in 139 patients with DS

	1-3 years	4-6 years	7-9 years	10-12 years	13-15 years (males)	13-15 years (females)
n	56	37	23	15	4	4
Range (mg/dl)	2.2-7.7	2.3-6.4	3.1-6.8	0.7-7.5	4.5-7.7	7-8.8
UA mean ± SD (mg/dl)	4.7 ± 1.32	4.6 ± 0.88	5 ± 0.97	5.5 ± 1.52	5.7 ± 1.37	8 ± 0.77
Hyperuricemia *n* (%)	22/56 (39.2)	4/37 (10.8)	4/23 (17.3)	5/15 (33.3)	1/4 (25)	3/4 (75)

DS: Down syndrome; UA: uric acid; SD: standard deviation.

TABLE 2 – Comparison of UA values and number of hyperuricemic patients according to age and gender

	Males	Females	*p*
1-3 years (*n* = 56)			
UA mean ± SD (mg/dl)	4.7 ± 1.36	4.7 ± 1.32	1*
Hyperuricemic *n* (%)	10/23 (43.4)	12/33 (36.6)	0.59**
4-6 years (*n* = 37)			
UA mean ± SD (mg/dl)	4.7 ± 0.9	4.5 ± 0.87	0.62*
Hyperuricemic *n* (%)	2/23 (8.6)	2/14 (14.2)	0.62§
7-9 years (*n* = 23)			
UA mean ± SD (mg/dl)	5.1 ± 1.05	5 ± 0.94	0.81*
Hyperuricemic *n* (%)	2/10	2/13	1§
10-12 years (*n* = 15)			
UA mean ± SD (mg/dl)	5.7 ± 0.68	5.4 ± 2.04	0.69*
Hyperuricemic *n* (%)	1/7 (14.2)	4/8 (50)	0.28§
13-15 years (*n* = 8)			
UA mean ± SD (mg/dl)	5.7 ± 1.37	8 ± 0.77	0.02*
Hyperuricemic *n* (%)	1/4	3/4	0.48§

*UA: uric acid; SD: standard deviation; *unpaired t-test; **chi squared test; §Fisher test.*

Hyperuricemia may result from an increased production of UA or from its decreased renal excretion[5]. In DS there is some evidence that hyperuricemia is due to increased production[5]. Zitnanová *et al*. (2004)[5] demonstrated that levels of a UA precursors such as hypoxanthine and xanthine were significantly lower in DS than in controls, suggesting that they have an increased rate of transformation to UA.

High UA has been shown to be an independent risk factor for various lifestyle-related diseases[17-21]. In American children, increased UA serum concentrations have been linked to carotid atherosclerosis by Pacifico *et al*. (2009)[19]. The KOALA Birth Cohort Study[18], which studied 246 school-age children, noted that values of serum UA and the ratios of UA/xanthine and xanthine/hypoxanthine were significantly associated with high blood pressure. Others have observed association of high UA levels with components of the metabolic syndrome[21]. So, the high rate of hyperuricemic DS children as seen in the present study may be implicated in future atherosclerotic complications and needs to be taken into account. Nevertheless, there are no studies demonstrating the value of treatment of hyperuricemia in this context.

Abdominal ultrasound showed no cases of nephrolithiasis in our patients. The occurrence of gallstones was similar to that observed in another study in Brazil that found 6.9% of lithiasis in DS children[22]. These patients should be monitored with serial abdominal ultrasound. In most cases, there is spontaneous resolution.

This study has several limitations, including its retrospective design and all weaknesses that this kind of design presents. In addition, we have no controls, as we chose not to draw blood from healthy children to have them. However, it does show the high rate of hyperuricemia in the studied children and the need to better study its repercussions into adulthood and the value of its treatment.

In summary, we found a high rate of hyperuricemia in children with DS that equally affects both sexes, except in the age range of 13-15 years, in which it was more common in females.

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