

## Original Article

# Serum Uric Acid in Children with Down Syndrome

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## Abstract

**Background:** Down syndrome (DS) is the most common chromosomal abnormality. Children with DS have elevated serum uric acid (UA) levels.

**Objective(s):** The aim of the present study was to estimate the serum UA levels in children with DS and compare it with the levels in normal children.

**Methods:** A case control study was conducted on 200 children at Alexandria University hospital, divided into two groups. Group I: included 100 children with DS (cases). Group II: included 100 healthy children as a control group. Children of both groups were subjected to history taking, clinical examination, renal function tests and serum UA estimation.

**Results:** 5% of patients had upper normal, 16% had high serum UA levels. None of the children in the control group had upper normal or high serum UA levels. This was statistically significant. Mean serum UA in patients was significantly higher than in the control children. There was a statistically significant positive correlation between serum UA and patients' age. No statistically significant correlation between serum UA and gender was detected in both groups.

**Conclusion:** Serum UA was significantly higher in children with DS than in controls. There was a significant positive correlation between serum UA and patients' age.

**Keywords:** Down syndrome, serum uric acid, children

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## INTRODUCTION

Down syndrome (DS) is the most common chromosomal abnormality and neurodevelopmental genetic disorder with incidence of 1:750 to 1:1000 live births.<sup>(1, 2)</sup> It is also the commonest genetic cause of mental retardation.<sup>(3)</sup> The etiology of DS is extra copy of the chromosome 21. In most cases (95%), this extra copy is maternally derived due to non-disjunction. In about 1- 5% of cases with DS this extra copy is due to translocation or mosaicism. Translocation is not affected by the maternal age and occurs in about 1-4% of cases. Mosaicism is present in about 1.3–5% of cases and has a milder phenotype.<sup>(4-7)</sup>

DS is associated with a variety of clinical features, which include small head, flattened occiput, upward slanting eyes, epicanthic fold, brush field spots, flat nasal bridge, low set small ears, small mid-face and maxilla, small mouth and relatively large protruding tongue, micrognathia, nuchal skin fold, cranio-cervical instability and hypermobility, broad small hands, short fingers, simian crease. Also; mental retardation, joint hyperflexibility, hypotonia, congenital anomalies of different organ systems as: cardiovascular and

digestive systems, autoimmune disorders and hematological abnormalities.<sup>(3, 8)</sup>

Many researchers studied the serum uric acid (UA) in children with DS, some of them reported elevation in the serum UA in those children, as children with DS are exposed to chronic oxidative stress (OS) which affects their development and leads to their aging, as trisomic cells are more sensitive to OS than normal cells. This sensitivity of the trisomic cells may be due to the increased production and metabolism of hydrogen peroxide due to the overexpressed gene by the trisomy state or to another unknown factor. Also, there is chromosomal imbalance of the genes located on chromosome 21 and abnormal expression of trisomic gene, in association with the responses to some environmental stimuli that might alter expression of the disomic genes. So, children with DS are more vulnerable to OS. OS is known to occur in DS from the very early stages during the embryonic development.<sup>(9-11)</sup>

Hyperuricemia was found to be a risk factor for various lifestyle-related diseases. There is association between increased UA concentrations and presence of metabolic syndrome, carotid atherosclerosis, renal failure and high blood pressure in children which

persist into adulthood.<sup>(12,13)</sup> That is why the level of serum UA has to be measured from early childhood in patients with DS to prevent the development of these diseases and their progression into adulthood.<sup>(14)</sup>

The aim of the present work was to study the serum UA levels in children with DS and compare it with the levels in normal children. Also, to study possible risk factors for the high serum UA levels in those children.

## METHODS

A case control study was conducted at Alexandria University Children's Hospital (AUCH). Epi Info 7 was used for sample size calculation, based on a previous research which reported 32.7% prevalence of hyperuricemia among children with Down syndrome.<sup>(14)</sup> The minimum required sample size for each group was 32 patients to achieve 80% study power, and 95% confidence limits. The study was conducted on 200 children, divided into two groups. Group I: included 100 children with DS, attending the genetics clinic in the Pediatrics department. Group II: included 100 healthy children matching in age and gender as a control group. Inclusion criteria: Age up to 12 years and consent from the caregiver for participation. Exclusion criteria: Having conditions that affect serum uric acid concentration (as renal diseases). Both studied groups were subjected to: full history taking with data collection of age, gender, presence of chronic diseases, parental consanguinity, and complete clinical examination. Karyotyping for children with DS who haven't done karyotyping before to confirm the diagnosis of DS.<sup>(15)</sup> Laboratory investigations including: renal function tests (blood urea nitrogen (BUN), serum creatinine); to exclude renal impairment that can cause hyperuricemia in children with DS.<sup>(16)</sup> Estimation of serum uric acid level by colorimetric method.<sup>(17)</sup> Both tests were done by: collection of 4 milliliters of venous blood from each patient by sterile venipuncture, then delivered in a plain glass tube labeled with the patient's name and serial number. After blood coagulation and centrifugation at 3000 rpm for 15 minutes, serum was collected and was divided into two parts. One part was used for performing renal function tests, and the other part was stored at -20°C till assay of serum uric acid level.

Raw data were coded and entered into statistical package for social sciences system files (SPSS package version 24). Analysis and interpretation of data were conducted. A  $p < 0.05$  levels were used as the cut off value for statistical significance.

### Ethical considerations

The study protocol was approved by the Ethical committee of Faculty of Medicine, University of

Alexandria. The caregivers were asked to provide written consents for their children to take part in the study, after explaining the purpose of the study. All data and information from the participants were kept confidential.

## RESULTS

The study was carried out on 200 children: 100 children with DS (cases) and 100 healthy children of matching age and gender (controls). There was no statistically significant difference between the two groups regarding age and gender ( $p = 0.595$ ,  $p = 0.775$  respectively). (Table 1)

**Table 1: Comparison between the cases and controls according to gender and age**

	Cases (n = 100)		Controls (n = 100)		Test of significance (p)
	No.	%	No.	%	
<b>Gender</b>					
Male	59	59	56	56	$X^2 = 0.184$ ( $p = 0.775$ )
Female	41	41	44	44	
<b>Age (months)</b>	30.78 ± 32.99		33.5 ± 33.7		$t = 0.585$ ( $p = 0.595$ )

$X^2$ : Chi square test

t: independent t-test

Regarding associated chronic diseases: 63% of patients with DS had associated chronic diseases mainly congenital cardiac defects (47% of patients) while only 16% of controls had associated chronic diseases. (Table 2).

**Table 2: Comparison between the cases and controls according to associated chronic diseases**

Chronic diseases present	Cases (n = 100)		Controls (n = 100)		Test of significance (p)
	No.	%	No.	%	
<b>Do not have chronic disease</b>	37 <sup>b</sup>	37	84 <sup>a</sup>	84	
<b>Have chronic disease</b>	63	63	16	16	
• Cardiac Defect	47 <sup>b</sup>	47	3 <sup>a</sup>	3	(MCP = 0.005*)
• Favism	0 <sup>a</sup>	0	1 <sup>a</sup>	1	
• Asthma	2 <sup>a</sup>	2	3 <sup>a</sup>	3	
• Hypothyroidism	4 <sup>b</sup>	4	0 <sup>a</sup>	0	
• Epilepsy	1 <sup>a</sup>	1	1 <sup>a</sup>	1	
• Squint	2 <sup>a</sup>	2	0 <sup>a</sup>	0	
• DM	1 <sup>a</sup>	1	0 <sup>a</sup>	0	
• laryngeomalacia	1 <sup>a</sup>	1	0 <sup>a</sup>	0	
• Iron deficiency anemia	0 <sup>b</sup>	0	8 <sup>a</sup>	8	
• > one disease	5 <sup>b</sup>	5	0 <sup>a</sup>	0	

a,b; Different letters indicate significant difference between column proportions using Bonferroni test

Both groups were clinically stable by clinical examination.

Serum uric acid was normal in 79% of children with DS and in 95% of controls. 5% of children with DS had upper normal levels of serum UA and 16% of

them had high serum uric acid level, while no one in the control group had upper normal or high serum UA levels. This was statistically significant ( $p < 0.0001$ ). (Table 3)

**Table 3: Comparison between the cases and controls according to the serum uric acid level**

Serum uric acid	Cases (n=100)		Controls (n=100)		Test of significance (p)
	No.	%	No.	%	
Low	0	0	5	5	
Normal	79	79	95	95	
Upper Normal	5	5	0	0	(MCP < 0.0001*)
High	16	16	0	0	

MCP: Monte Carlo Exact  $p$  value

The mean serum uric acid in children with DS ( $3.99 \pm 1.37$  mg/dl) was significantly higher than in controls ( $2.6 \pm 0.63$  mg/dl) ( $p < 0.0001$ ). (Table 4)

**Table 4: Comparison between the cases and controls according to the mean serum uric acid level**

Serum uric acid (mg/dl)	Cases (n = 100)	Controls (n = 100)	Test of significance (p)
Mean $\pm$ SD	$3.99 \pm 1.37$	$2.6 \pm 0.63$	$t = -9.204$ ( $p < 0.0001^*$ )

\*: Statistically significant

There was no statistically significant difference between the two studied groups regarding BUN and serum creatinine. (Table 5)

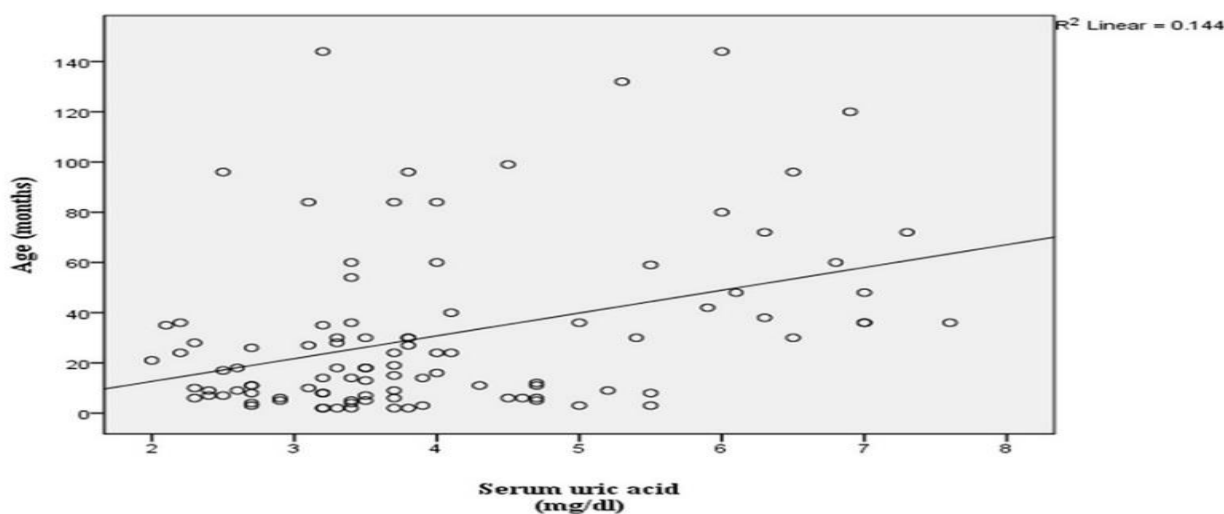
**Table 5: Comparison between the cases and controls according to blood urea and serum creatinine**

	Cases (n = 100) Mean $\pm$ SD	Controls (n = 100) Mean $\pm$ SD	Test of significance (p)
Blood urea (mg/dl)	$10.16 \pm 2.82$	$9.94 \pm 2.68$	$t = -0.565$ ( $p = 0.573$ )
Serum Creatinine (mg/dl)	$0.43 \pm 0.15$	$0.47 \pm 0.16$	$t = -0.585$ ( $p = 0.56$ )

There was a statistically significant positive correlation between the serum UA and age in children with DS (cases) ( $p = 0.001$ ) as shown in figure 1. There was no significant correlation between the

serum UA and age in the control group.

There was no statistically significant difference between the mean of serum UA and gender in cases and controls ( $p = 0.512$  &  $p = 0.217$  respectively). (Table 6)



**Figure 1: Correlation between serum uric acid and age among children with Down syndrome**

**Table 6: Comparison between the mean values of the serum uric acid and gender in the two studied groups**

Groups	Male (n = 85)	Female (n = 115)	Test of significance (p)
Cases Serum uric acid (mg/dl) Mean $\pm$ SD	$4.1 \pm 1.36$	$3.9 \pm 1.4$	$t = 0.658$ ( $p = 0.512$ )
Controls Serum uric acid (mg/dl) Mean $\pm$ SD	$2.67 \pm 0.67$	$2.5 \pm 0.55$	$t = 1.24$ ( $p = 0.217$ )

## DISCUSSION

Many studies reported elevation in the serum UA in children with DS. It was found that serum UA levels are higher in those children than in normal children due to increased OS in them.<sup>(11,18)</sup>

The present study gives evidence of the increased serum UA level in children with DS. We highlight the significance of studying serum UA in this group of children.

The serum Uric acid and the mean UA levels were significantly higher in children with DS than control children.

This is in concordance with the study by Kashima *et al.*<sup>(14)</sup> who found that hyperuricemia occurred in 32.7% of children with DS and was significantly higher than the controls. Also, Zitnanová *et al.*<sup>(19)</sup> who reported that children with DS have elevated serum uric acid levels compared with controls.

This also matches Málaga *et al.*<sup>(16)</sup> who studied sixty nine patients (37 boys, 32 girls) aged between 12 months and 24 years (median age: 9.7 years). The results showed that eight patients (11.6%) presented with hyperuricemia. Kaufman and O'Brien<sup>(20)</sup> also found that the mean serum UA was higher in children with DS compared to mentally retarded controls without DS from the same institution. This seemed to be a highly significant increase. Also, Pant *et al.*<sup>(21)</sup> studied the levels of serum UA in 280 children with DS. They found significant higher serum UA levels in those children compared to 298 control subjects. And, Niegawa *et al.*<sup>(22)</sup> concluded that children with DS, in their study, have higher incidence of hyperuricemia than normal children.

On the other hand, de Sousa *et al.*<sup>(23)</sup> showed no significant difference in levels of UA in children with DS. This difference may be attributed to the small populations involved in the study (n = 30 patients with DS).

In the pediatric age group, chronic hyperuricemia may be associated with underlying diseases, as: kidney diseases, inborn errors of metabolism or genetic disorders.<sup>(24)</sup>

In the present study, children with diseases that could influence the serum level of UA (mainly renal disease) were excluded. All studied children in both groups had normal BUN and serum creatinine levels with no statistical significance difference between the two groups.

In the present study, there was a significant positive correlation between the serum UA and the age of children in group I; the older the age of the child with DS, the higher the serum level of UA.

This is in concordance with Niegawa *et al.*<sup>(22)</sup> who found that the levels of UA was positively associated with age.

In contrary, the study by Kashima *et al.*<sup>(14)</sup> compared 52 children with DS from 1-15 years of age, with controls (age-matched). They found no significant correlation between the serum uric acid & age. This difference in age significance may be attributed to the smaller sample size in their study.

On the other hand, in the present study, there was no significant correlation between the serum UA levels and the gender of children in group I.

On the contrary; the studies by Kashima *et al.*<sup>(14)</sup> showed positive correlation between hyperuricemia and male gender. Also, Niegawa *et al.*<sup>(22)</sup> observed that the levels of UA were higher in males with DS than in females (approximately 32% and 10%, respectively).

## CONCLUSION AND RECOMMENDATIONS

The present study gives evidence of the increased serum UA level in children with DS. Serum uric acid was significantly higher in children with DS than in control children. There was a positive significant correlation between serum UA in children with DS and their age. The age of the child with DS is a risk factor for higher UA level.

It is recommended to follow up the serum levels of infants and children with DS regularly for early detection and management of hyperuricemia.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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