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

INTRODUCTION

Down syndrome (DS) is the most common chromosomal abnormality and neurodevelopmental genetic disorder with incidence of 1:750 to 1:1000 live births.1–2 It is also the commonest genetic cause of mental retardation.3 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.4–7

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.3–8

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 an 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.9–11

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
persists into adulthood.\textsuperscript{(12,13)} 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.\textsuperscript{(14)}

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.\textsuperscript{(14)} 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.\textsuperscript{(15)} Laboratory investigations including: renal function tests (blood urea nitrogen (BUN), serum creatinine); to exclude renal impairment that can cause hyperuricemia in children with DS.\textsuperscript{(16)} Estimation of serum uric acid level by colorimetric method.\textsuperscript{(17)} 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 \( (p = 0.595, p = 0.775 \text{ respectively}) \). (Table 1)

|                      | Cases \( (n = 100) \) | Controls \( (n = 100) \) | Test of significance \( (p) \) |
|----------------------|------------------------|---------------------------|-------------------------------|
| **Gender**           |                        |                           |                               |
| Male                 | 59                     | 56                        | \( \chi^2 = 0.184 \ (p = 0.775) \) |
| Female               | 41                     | 44                        |                               |
| **Age** (months)     | 30.78 ± 32.99          | 33.5 ± 33.7               | \( t = 0.585 \ (p = 0.595) \) |

\( \chi^2 \): 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).

| Chronic diseases present | Cases \( (n = 100) \) | Controls \( (n = 100) \) | Test of significance \( (p) \) |
|--------------------------|-----------------------|---------------------------|-------------------------------|
| Do not have chronic disease | 37\%                 | 37\%                      |                               |
| Have chronic disease     |                       |                           |                               |
| Cardiac Defect           | 63                    | 63                        |                               |
| Asthma                   | 47\%                  | 47\%                      |                               |
| Hypothyroidism           | 2\%                   | 2\%                       |                               |
| Epilepsy                 | 1\%                   | 1\%                       |                               |
| Squint                   | 2\%                   | 2\%                       |                               |
| DM                       | 1\%                   | 1\%                       |                               |
| Iaryngeomalacia          | 1\%                   | 1\%                       |                               |
| Iron deficiency anemia   | 0\%                   | 0\%                       |                               |
| \( > 1 \) one disease    | 5\%                   | 5\%                       | \( \text{MCP} = 0.005\*)      |

\( a,b \): 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. | %   |               | MCP: Monte Carlo Exact p value |
| Low             | 0   | 0   | 5   | 5   |               |                           |
| Normal          | 79  | 79  | 95  | 95  | (MCP < 0.0001*) |
| Upper Normal    | 5   | 5   | 0   | 0   |               |                           |
| High            | 16  | 16  | 0   | 0   |               |                           |

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 ± SD | Controls (n = 100) Mean ± SD | Test of significance (p) |
|----------------------|---------------------------|-----------------------------|--------------------------|
| Blood urea (mg/dl)   | 10.16 ± 2.82              | 9.94 ± 2.68                 | t = -0.565 (p = 0.573)   |
| Serum Creatinine (mg/dl) | 0.43 ± 0.15          | 0.47 ± 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.

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

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

*: Statistically significant

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

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

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 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       | Serum uric acid (mg/dl) Mean ± SD | Male (n = 85) | Serum uric acid (mg/dl) Mean ± SD | Female (n = 115) | Test of significance (p) |
|--------------|----------------------------------|---------------|-----------------------------------|------------------|--------------------------|
| Cases        | 4.1 ± 1.36                       |               | 3.9 ± 1.4                         |                  | t = 0.658 (p = 0.512)    |
| Controls     | 2.67 ± 0.67                      | 2.5 ± 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.\(^\text{[11,18]}\)

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.\(^\text{[14]}\) who found that hyperuricemia occurred in 32.7% of children with DS and was significantly higher than the controls. Also, Zitanová et al.\(^\text{[19]}\) who reported that children with DS have elevated serum uric acid levels compared with controls.

This also matches Málaga et al.\(^\text{[16]}\) 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 \(^\text{[20]}\) 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.\(^\text{[21]}\) 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.\(^\text{[22]}\) concluded that children with DS, in their study, have higher incidence of hyperuricemia than normal children.

On the other hand, de Sousa et al.\(^\text{[23]}\) 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.\(^\text{[24]}\)

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.\(^\text{[22]}\) who found that the levels of UA were positively associated with age.

In contrary, the study by Kashima et al.\(^\text{[14]}\) 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.\(^\text{[14]}\) showed positive correlation between hyperuricemia and male gender. Also, Niegawa et al.\(^\text{[22]}\) 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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REFERENCES

1. Antonarakis SE, Skotko BG, Rafii MS, Strydom A, Pape SE, Bianchi DW, et al. Down syndrome. Nat Rev Dis Primers. 2020;6(1):9.
2. Karmiloff-Smith A, Al-Janabi T, D’Souza H, Giro J, Massand E, Mok K, et al. The importance of understanding individual differences in Down syndrome. F1000Res. 2016;5:F1000.
3. Ram G, Chinen J. Infections and immunodeficiency in Down syndrome. Clin Exp Immunol. 2011;164(1):9-16.
4. Korbel JO, Tirosich-Wagner T, Urban AE, Chen XN, Kasowski M, Dai L, et al. The genetic architecture of Down syndrome phenotypes revealed by high-resolution analysis of human segmental trisomies. Proc Natl Acad Sci U S A. 2009;106(29):12031-6.
5. Papavassiliou P, Charalsawadi C, Rafferty K, Jackson-Cook C. Mosaicism for trisomy 21: a review. Am J Med Genet A. 2015;167a(1):26-39.
6. Sherman SL, Freeman SB, Allen EG, Lamb NE. Risk factors for nondisjunction of trisomy 21. Cytogeten Genome Res. 2005;111(3-4):273-80.
7. Coppeè F. Risk factors for Down syndrome. Arch Toxicol.
8. Bull MJ. Health supervision for children with Down syndrome. Pediatrics. 2011;128(2):393-406.
9. Garlet TR, Parisotto EB, de Medeiros GdS, Pereira LC, Moreira EA, Dalmarco EM, et al. Systemic oxidative stress in children and teenagers with Down syndrome. Life Sci. 2013;93(16):558-63.
10. Subba Rao K. Mechanisms of disease: DNA repair defects and neurological disease. Nat Clin Pract Neurol. 2007;3(3):162-72.
11. Campos C, Guzmán R, López-Fernández E, Casado A. Urinary uric acid and antioxidant capacity in children and adults with Down syndrome. Clin Biochem. 2010;43(3):228-33.
12. Saito E, Okada T, Abe Y, Karama M, Yonezawa R, Karomori Y, et al. Non-high-density Lipoprotein Cholesterol Levels in Japanese Obese Boys with Metabolic Syndrome. J Atheroscler Thromb. 2016;23(1):105-11.
13. Li C, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes, and hyperuricemia. Curr Opin Rheumatol. 2013:25(2):210-6.
14. Kashima A, Higashiyama Y, Kubota M, Kawaguchi C, Takahashi Y, Nishikubo T. Children with Down's syndrome display high rates of hyperuricaemia. Acta Paediatr. 2014;103(8):e359-64.
15. Bacino CA, Lee B. Cytogenetics. In: Kliegman RM, Geme JS, Blum NJ, Shah SS, Robert C, Wilson KM, (eds). Nelson textbook of Pediatrics. London: Elsevier; 2019. Chapter 98.
16. Málaga S, Pardo R, Málaga I, Orejas G, Fernández-Toral J. Renal involvement in Down syndrome. Pediatr Nephrol. 2005;20(5):614-7.
17. Rice EW, Grogan BS. 1960 survey of clinical chemistry procedures used by members of the American Association of Clinical Chemists. Clin Chem. 1962;8:181-93.
18. Houston M, Chumley P, Radl R, Rubbo H, Freeman BA. Xanthine oxidase reaction with nitric oxide and peroxynitrite. Arch Biochem Biophys. 1998;355(1):1-8.
19. Zímanová I, Korytáre P, Anuomia O, Sustrová M, Garaiová I, Machová J, et al. Uric acid and allantoin levels in Down syndrome: antioxidant and oxidative stress mechanisms? Clin Chim Acta. 2004;341:139-46.
20. Kaufman JM, O'Brien WM. Hyperuricemia in mongolism. N Engl J Med. 1967;276(17):953-6.
21. Pant SS, Mover HW, Krane SM. Hyperuricemia in Down's syndrome. J Clin Endocrinol Metab. 1968;28(4):472-8.
22. Niegawa T, Takitani K, Takaya R, Ishiro M, Kuruyanagi Y, Okasora K, et al. Evaluation of uric acid levels, thyroid function, and anthropometric parameters in Japanese children with Down syndrome. J Clin Biochem Nutr. 2017;61(2):146-52.
23. de Sousa MC, Vieira RB, Dos Santos DS, Carvalho CA, Camargo SE, Mancini MN, et al. Antioxidants and biomarkers of oxidative damage in the saliva of patients with Down's syndrome. Arch Oral Biol. 2015;60(4):600-5.
24. Ito S, Torii T, Nakajima A, Iijima T, Murano H, Horisuchi H, et al. Prevalence of gout and asymptomatic hyperuricemia in the pediatric population: a cross-sectional study of a Japanese health insurance database. BMC Pediatr. 2020;20(1):481.