

## **Meatal Stenosis and Atopic Condition: A Pilot Study Demonstrating a Possible Unidentified Etiology**

**Nastaran Sabetkish<sup>1,2</sup>, Zahra Pourpak<sup>2</sup>, Abdol-Mohammad Kajbafzadeh<sup>1</sup>, Raheleh Shokouhi Shoormasti<sup>2</sup>, and Mahsa Jafari<sup>2</sup>**

<sup>1</sup> *Section of Tissue Engineering and Stem Cells Therapy, Pediatric Urology and Regenerative Medicine Research Center, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran*  
<sup>2</sup> *Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran*

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### **ABSTRACT**

Meatal stenosis (MS) is known as one of the most frequent complications of circumcision. In the present study, we aimed to find any possible relationship between MS and allergic disorders.

A total of 36 children with a mean±SD age of 5.84±2.03 years were referred with MS and an atopic background even in themselves or in one of their family members (Group A). There were also age-matched controls with a mean±SD age of 5.70±2.17 years who were referred to our center with allergic symptoms and no urinary complaints (Group B, n=17). The RIDA qLine allergy and allergy explorer (ALEX) tests were performed for all patients to find possible allergen sensitization.

Laboratory findings revealed that IgE-sensitization to the main food and aeroallergens in Group A (with the chief complaint of MS in whom a mild atopic condition was found during concise medical history taking) were very similar to the control group with no significant difference (except for ryegrass which was higher in the control group). Although total IgE level was considerably higher in group B compared to group A, food sensitization to cow's milk and β-lactoglobulin was higher in asthmatic patients of group A compared to the controls.

It seems that not all patients with MS should be considered as a complication of circumcision and undergo a surgical procedure for correction of the stenosis. Further investigations are required to determine the role of concise medical history taking and proper treatment of the allergic disorder to reduce failed surgical attempts in atopic boys with MS.

**Keywords:** Asthma; Atopic dermatitis; Food hypersensitivity; Male circumcision; Urology

### **INTRODUCTION**

Circumcision as a frequent ancient procedure<sup>1</sup> has

been the focus of attention due to its possible role in the formation of meatal stenosis (MS). According to a recent systematic review and meta-analysis, MS

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**Corresponding Author:** Abdol-Mohammad Kajbafzadeh, MD;  
Section of Tissue Engineering and Stem Cells Therapy, Pediatric  
Urology and Regenerative Medicine Research Center, Children's

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Medical Center Hospital, Tehran University of Medical  
Sciences, Tehran, Postal Code: 1419433151, Iran. Tel/ Fax: (+98 21)  
6656 5400, E-mail: kajbafzd@sina.tums.ac.ir

occurred in about 0.7% of circumcised males;<sup>2</sup> while other studies have reported a higher prevalence.<sup>3,4</sup> The incidence of symptomatic MS has been estimated to be about 3%.<sup>5</sup>

The underlying etiology of MS is vague while meatitis and meatal ischemia have been suggested as possible causes of MS after circumcision<sup>6</sup>. Some studies have suggested the exposure of the penile glans and meatus with environmental factors such as feces, ammoniacal urine, underwear, and diaper as the potential reasons for chronic irritation and s further adherence to the epithelial lining.<sup>7-10</sup>

Surgical intervention and creating a ventral incision of the meatus is the classic and definite management of MS; however, low rates of restenosis and the require for reoperation have been reported.<sup>11, 12</sup> Nevertheless, according to a large number of patients with several previous failed meatotomy; we are thinking of other possible unknown etiologies. We hypothesized that the urine of atopic patients may contain inflammatory materials; causing stenosis. Additionally, dermatitis in the genital area that may be caused both by the urine contents and the underwear materials, could induce allergic reaction and further stenosis in this subgroup of patients.

In our recent study, patients with MS had a significantly higher likelihood of suffering from allergic reactions as compared with those being referred to the urology department due to other etiologies.<sup>13</sup> The objective of the current study was to assess the possible role of atopic disorders in the formation of stenosis in boys with symptomatic meatal stenosis, inflamed urinary meatus, and a positive history of atopy.

## MATERIALS AND METHODS

After obtaining the approval statement from the ethics committee of Tehran University of Medical Sciences and obtaining a signed informed consent from all parents, a total of 36 male boys with symptoms of MS and a positive history of atopy in themselves or their family members (Group A) were referred to pediatric urology and regenerative medicine research center (PURMRC) over 2 years (2017-2019). This study was ethically approved by the Tehran University of Medical Sciences (Ethical Number 48965).

This population was chosen from a total number of 154 cases who were referred to our center with MS

with or without a positive history of atopy (24.67%). All patients had a positive history of circumcision in the early infancy period and had inflammation around the meatus in clinical examination. Children aged 2-12 years who were previously toilet trained and were able to urinate at request were eligible for recruitment. Patients with penile or meatal abnormality such as penile curvature or any type of hypospadias, underlying neurologic abnormality, concomitant psychiatric problem, those who did not complete the study protocol, and children who had undergone a previous failed surgical procedure for correction of MS were excluded from the study. After recording demographic and clinical data including the age of circumcision, lower urinary tract symptoms, voiding patterns, the caliber of the meatus, operation procedures, history of any kind of allergic reactions, and family history of atopic diseases, further assessments were performed in regards of allergic disorders. A total of 17 sex- and age-matched controls were referred to immunology, asthma, and allergy research institute (IAARI) with allergic symptoms and no urinary complaints (Group B).

Total IgE level (ELISA, Pishtazteb, Iran) and Eosinophil count of patients were evaluated for both groups. To assess the specific IgE (allergic sensitization) to allergens, RIDA qline Allergy (R-Biopharm Company, Germany) was performed for all Group A patients. Moreover, the Macroarraytest (ALEX Allergy Explorer)(Macro-array Diagnostics, Austria) was done for 28 out of 36 patients in Group A and all subjects in Group B. RIDA qline Allergy is an Immunoblotting test on nitrocellulose membrane to assess specific IgE to food and aeroallergens extracts. Macroarray (ALEX) is a multiplex test based on nano-bead technology for the simultaneous measurement of specific IgE to allergenic extracts and molecules. A value of more than 0.35 IU/mL and 0.30 kUA/L was considered a positive result for RIDA qline Allergy and ALEX Allergy Explorer, respectively. The subjects with at least one positive specific IgE test were considered as "sensitized patients".

## Statistical Analysis

IBM SPSS software version 20(IBM Corporation, NY, USA) was used to analyze the data. To evaluate the normality of quantitative variables, Kolmogorov-Smirnov was used. Mean and Standard Deviation (SD) or Median (Q1, Q3) were calculated. The difference between quantitative variables in two groups was

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determined; using the independent t-test or Mann-Whitney test. A chi-square test or Fisher exact test was applied to determine the relationship between two categorical variables. Graphpad Prism 6 software (Graphpad Software Inc., La Jolla, CA, USA) was utilized to draw the graphs.

### RESULTS

A total of 36 atopic boys with meatal stenosis and 17 aged- and sex-matched cases with allergic diseases have entered this study. The demographic data are summarized in Table 1. Allergic diseases included asthma (n=22), atopic dermatitis (n=19), and allergic rhinitis (n=6) in group A. In the control group 11 children had respiratory symptoms; while skin manifestations were detected in 7 cases. The mean age of patients and controls was 5.84 (SD=2.03) and 5.70 (SD=2.17) years, respectively. The median of total IgE levels was significantly higher in the control group ( $p=0.005$ ); while eosinophil count did not show any significant difference among groups ( $p=0.09$ ). The age at circumcision ranged from 1 to 5 months (mean: 2.5). All patients were referred to our center due to a high-velocity stream of urine and a narrow stream during urination that was noted by their parents. Twenty-nine out of 36 boys were forced to sit back from the toilet bowl to avoid urine spillage. None of the patients experienced hematuria. Frequency, dysuria, and UTI were detected in 27, 9, and 5 patients, respectively. The mean patients' age at presentation was 7.2 years (range:

4 to 8). The interval of circumcision and the onset of symptoms varied from 4.5 to 8.3 years (mean: 78.2 months).

As the results of specific IgE assay to whole extracts and allergenic molecules of food and aero-allergens showed the most prevalent sensitization to food allergens in group A included cow's milk (33.3%), kiwi Cysteine protease (Act d 1) (29.6%), and peanut nsLTP (Ara h9) (25.9%). On the other hand, Ragweed Pectate Lyase (Amb a 1) (29.6%) (Class 1), Defensin, Amb a 4 (25.9%) (Class 1), and the major allergenic molecule of *Cupressus arizonica* (cup a 1) (14.8%) were considered as the most common sensitized inhalant molecules in Group A.

Another finding was the higher frequency of IgE-sensitization to food allergens in group B with skin symptoms compared to group A. According to the results, the allergic sensitization to cow's milk (42.1%), Kiwi Cysteine protease (Act d 1) as well as nsLTP of peanut, kiwi, and peach (38.5%) were most common in group A with skin manifestations.

Figure 1 is presenting the results of allergic sensitization to food and aero-allergens in patients and controls. Specific IgE positivity to Cow's milk,  $\beta$ -lactoglobulin, Kiwi, Cysteine protease (Act d 1), and ns LTP of peanut, kiwi, and peach demonstrated the highest frequency in case patients with asthma symptoms. Interestingly, the case group with asthmatic symptoms showed a higher prevalence of food sensitization rather than control individuals with asthma symptoms.

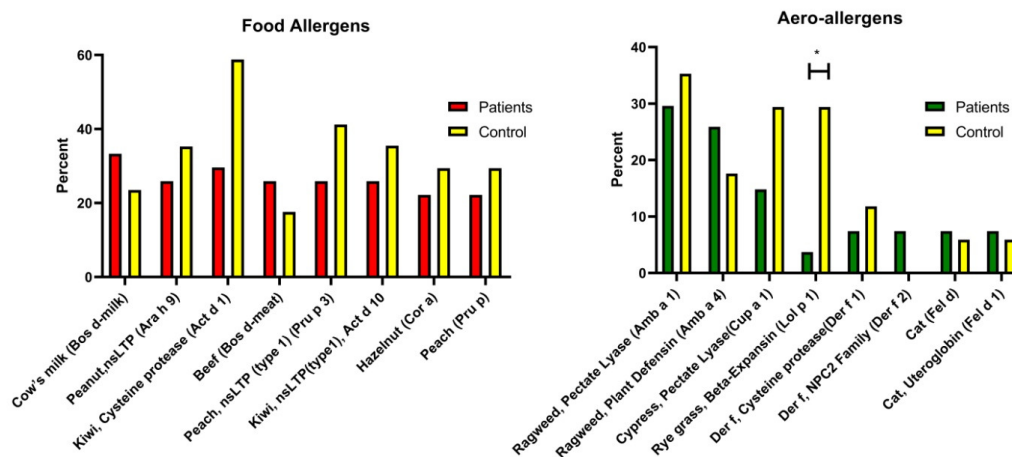


Figure 1. Allergic sensitization to food and aero-allergens in patients and controls (\* $p<0.05$ )

**Table 1. Demographic data of patients with meatal stenosis and atopic subjects**

	<b>Patients n=36</b>	<b>Controls n=17</b>	<b>p</b>
Age (years) Mean $\pm$ SD	5.84 $\pm$ 2.03	5.70 $\pm$ 2.17	0.82
Skin symptoms N (%)	19 (52.8%)	7 (41.2)	0.43
Respiratory symptoms N (%)	28 (77.8)	11 (64.7)	0.33
Total IgE Median (Q1, Q3)	10.05 (3.91, 37.61)	72.03 (30.13, 1088)	<b>0.005</b>
Eosinophils Count	158	332	
Median (Q1, Q3)	(80.75, 261.75)	(86.75, 584.5)	0.09

## DISCUSSION

In this study, a total of 36 boys were referred with MS, and atopic history. Meatotomy was postponed in these children due to the low grade of MS and with the hypothesis that if the stenosis is caused by an atopic background, complete resolution of all symptoms would not occur after surgical procedure.

National rates of male circumcision as the most common surgical procedure performed in the United States have declined from 65% in 1979 to 58% in 2010 following the 1999 AAP policy revision; stating inadequate evidence to advocate regular newborn circumcision despite its prospective medical benefits.<sup>14</sup> Symptomatic MS which is known as one of the complications of circumcision is seen in 3% to 8% of boys.<sup>15</sup> A meatal diameter of less than 5Fr in circumcised children aged between 5 and 10 years is known as asymptomatic MS found in up to 20% of patients.<sup>16</sup> Bazmamoun et al found that applying ointment after each diaper change for 6 months to decrease the trauma to the exposed urethral epithelium from clothing, has significantly decreased the incidence of MS.<sup>7</sup>

It is not far from the mind that the characteristics and location of allergic inflammation are dissimilar at different ages.<sup>17</sup> Lugosi et al found that measurement of urinary eosinophil protein X (U-EPX) helped monitor inflammation in childhood bronchial asthma and had a significant correlation with being symptomatic and having a poor pulmonary function.<sup>18</sup> Similar results were obtained in another study declaring that greater urinary level of EPX and serum level of eosinophil cationic protein (ECP) may reflect active atopic asthma while anti-inflammatory treatment probably may decrease their level as an indirect sign of airway inflammation normalization and improved lung function.<sup>19</sup> These findings are following the results of the current study in terms of the presence of activated

eosinophils that release cytotoxic granule compounds in the urinary system that may be a crucial factor in the formation of MS in atopic children. Majamaa et al assumed the release of eosinophil granular proteins in the gastrointestinal tract as a result of atopic dermatitis and food allergy even in the absence of clinical manifestations; causing increased concentrations of fecal EPX and ECP.<sup>20</sup> Because exposure to fecal is believed to have a possible role in the incidence of MS, the presence of such substances may trigger the formation of stenosis. So that treating the underlying disease may cure the urinary symptoms as well.

It has been shown that food-hypersensitive patients had a positive local allergic reaction despite a lack of systemic food-specific IgE; suggesting that there may be no correlation between the symptoms of food allergy and tissue-activated cells including eosinophils, T cells, and IgE-bearing cells.<sup>21</sup> This finding suggests that localized IgE-mediated response may not follow systemic changes and patients may suffer from local symptoms even when the serum evaluations are in normal condition. Similarly, we cannot rule out the role of localized allergic reactions in our atopic patients even in the presence of a low total IgE level and eosinophilic count. In other words, specific localized immune-mediated signals may be present in the urinary system of this subgroup of patients; resulting in MS and its further symptoms. The study of this possibility is recommended by the evaluation of certain markers such as U-EPX and urinary eosinophil counts.

Even though the pathophysiology of MS remains not completely understood, our recent preliminary study has revealed a significant relationship between the history of hypersensitivity and MS.<sup>13</sup> Accordingly, we found that persistent inflammation in the meatal area could result in scarring and further stenosis. So in this study, we decided to evaluate the laboratory

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findings of these cases. However, more surveys are on the way to elucidate the exact pathophysiology.

This pilot study although being novel and innovative has several limitations that have to be addressed in future cohort investigations. First of all, the low sample size of the present study needs to be eliminated in future larger studies. Additionally, atopic patients with MS were not compared with non-atopic controls suffering from MS. The outcomes of allergic management on regression of urinary symptoms and the recurrence of stenosis symptoms were not addressed. Though, we have designed a prospective cohort to evaluate the result of medication and avoidance strategies on the treatment of related urinary symptoms and uroflowmetry parameters.

In conclusion, the prevalence of allergic disorders seems to be higher in patients with MS; compared to those with other urologic complaints. If allergic disorders are proved to be the underlying cause of MS, its treatment has several benefits. Besides the cost benefits achieved with the prevention of general anesthesia and repeated surgeries in atopic patients, both the underlying atopic condition and the resultant urinary symptoms may be successfully controlled by using a simple anti-histamine allergic avoidance, or adequate elimination diet; using interdisciplinary strategies.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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