ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 09, pp.73860-73864, September, 2018

DOI: https://doi.org/10.24941/ijcr.30229.09.2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

INFLUENCE OF VESICO-URETERAL REFLUX ON GROWTH

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ARTICLE INFO

Article History:
Received 20th June, 2018
Received in revised form
27th July, 2018
Accepted 20th August, 2018
Published online 30th September, 2018

Key words:
Vesico-ureteral reflux,
Pyelonephritis,
Growth indices

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ABSTRACT

Vesico-ureteral reflux (VUR) is the most common urologic abnormality seen in children. It represents the backflow of urine from bladder to upper urinary structures due to a defect in closure of uretero-vesical junction. This condition predisposes children to repetitive pyelonephritis associated with renal scarring. Studies are continuously searching for the potential effect of VUR on growth. We aimed to assess growth indices: height z-score (HZ), Ideal body weight percent (IBWp) and percent of actual weight over median weight for age (MWAp) in children with VUR at presentation and at time of study and to compare them with those of children with pyelonephritis without VUR. We included children aged between 0 and 6 years old with a normal renal function admitted in our center for pyelonephritis. However, children with chronic diseases affecting growth were excluded. The children who met above criteria (112 children) were divided into 3 groups according to voiding cystourethrogram results: G1(VUR grade 1-2), G2(VUR grade 3 , 4 , 5) and G3 (no VUR). Our data showed no significant difference between the 3 groups concerning sex, age groups, consanguinity, gestational age, height and weight at birth. However, we noted a strong association between VUR and ESBL infection (p=0.0001), and history of previous pyelonephritis (p=0.0357). Growth indices HZ and MWAp were significantly lower in G2 than in other groups at presentation and at time of study (p=0.0001) for both. In contrast, no significant change was detected in IBWp neither at presentation nor at time of study. No significant association was found between reflux laterality and growth indices. We also noted a significant improvement in HZ (p=0.01) and in MWAp (p=0.0168) following surgical treatment, while no significant change was recorded in growth indices following antibiotic prophylaxis.

***Citation*: *HneinehRoula and Nicolas Georges* . 2018.** "Influence of vesico-ureteral reflux on growth", *International Journal of Current Research*, 10, (09), 73860-73864.

INTRODUCTION

Vesico-ureteral reflux (VUR) is the most urologic abnormality seen in childhood and accounting for up to one third of febrile urinary tract infections encountered in pediatric patients. It is defined as the backflow of urine from the bladder to upper urinary structures. This condition results from a defect in closure of uretero-vesical junction either due to a congenital short intravesical ureter (primary VUR) or a high pressure in the bladder (secondary reflux). Several risk factors were involved such as female sex, white race, age less than 2 years old and having a family history of VUR (TejMatto, 2017). A new study published in November 2017 in "American journal of renal physiology" by Fillion and al. suggested that newborns having a mutation in Osr1 (Odds related skipped 1) gene exhibit a 21% risk ofvesico-ureteral reflux (Fillion Marie-Lynn, 2017). Vesico-ureteral reflux predisposes children to repetitive urinary tract infection associated with renal scarring. As a result, the child will be at risk of long term hypertension and chronic kidney disease known as reflux nephropathy (Bogaert Guy, 2012), if vesico-ureteral reflux was not treated adequately. Moreover, in the last two decades, studies are continuously searching for the potential effect of vesico-ureteral reflux on growth. While normal growth was shown to be an important predictor of a good physical and mental health, a delayed growth may be the first sign of an underlying illness and may compromise self-esteem and well-being of the affected child. For this reason, we aimed to study growth indices in children with vesico-ureteral reflux at presentation and at time of the study, and to compare them with those who had an episode of pyelonephritis but without evidence of VUR on voiding cystourethrogram.

MATERIALS AND METHODS

Study design: We included in our study children aged between 0 and 6 years with a normal renal function at presentation, admitted to our center for pyelonephritis from January 2007 till December 2016, and who underwent voiding cystourethrogram three to four weeks following infection.

However, children with diabetes, or suffering from a chronic disease that affects growth such as coeliac disease or inflammatory bowel diseases were excluded. We had access to medical records of 112 children who met above criteria. We divided them into three groups according to voiding cystourethrogram results: G1(mild VUR), G2(moderate to severe VUR), G3(no VUR). We collected important parameters such as age at presentation, birth term, previous episode of pyelonephritis, weight and length/height at birth, at presentation and at time of study(December 2017).

Growth indices

For assessment of growth in children, we used three indices: Height Z score (HZ), ideal body weight percent (IBWp) and median body weight for age percent (MWAp). A child having a HZ below -2 is considered to have a short stature, while a HZ score above +2 indicates a long stature. IBWp is the percent of ideal body weight. Ideal body weight was measured according to the following method: Determining the weight percentile that is proportionate to height percentile for chronologic age using CDC (centers for disease control) growth charts. An ideal body weight percent less than 90% denoted a lean body, whereas an IBWp above 120% represented an obese child (Nichols Julieana, 2017), also known as weight for height index in other studies). On the other hand, MWAp is the percent of the weight of the child over median weight for age (50^{th} percentile according to CDC growth charts): It is an in dice that we have created.

Statistical Analysis

Dependent variables of our study were: HZ, IBWp and MWAp. Our data was analysed using SPSS 22 with a 5% risk of error. A p-value less than 0.05 indicated a significant result. Quantitative variables were expressed in mean+/- standard deviation, whereas qualititative variables were expressed in percentage. We used Chi square test for descriptive study (delivery mode, birth term, previous episode of pyelonephritis, age groups, sex, Organisms on urine culture and ESBL infections), and to compare growth indices growth indices between 3 groups, we used one way ANOVA. Moreover, to compare growth indices according to laterality of reflux, we used student t test. Last but not least, to assess the evolution of growth indices between presentation and time of study, we used paired t test.

RESULTS

Analysis of independent parameters: Table 1 shows socio-demographic characteristics of recruited children. We noticed a higher percentage of girls in the three groups (86.1% in G1, 66.7% in G2 and 70.6% in G3) without a significant difference in percentages between the three groups (p=0.12). Also, no significant difference in percentages of age groups was noticed between the three groups(p=0.094) and same for consanguinity(p=0.682). Table 2 shows parameters of children at birth:

No difference was detected between the three groups regarding birth term(p= 0.854), delivery mode (p=0.604), length and weight at birth(p=0.204 and p=0.931) respectively. Concerning history of previous episodes of febrile urinary tract infection, we detected a significant difference (p=0.0357) between children with vesico-ureteral reflux(G1+G2) and those without VUR. In fact, 58.9% of children with vesico-ureteral reflux reported previous episodes of febrile urinary tract infection vs 35.3% in children without VUR. (Table 3) Table 4 shows results of urine culture of children in the three groups. E.coli is the most common organism responsible for urinary tract infection in recruited children (72.2% in G1; 90.5% in G2 and 91.2% in G3). We found a significant difference in ESBL (extended spectrum β-lactamase) percentages between the three groups (p=0.0001) where 81.2% of children in G2 had ESBL infections.

Analysis of growth indices

Table 5 shows the three growth indices at presentation and at time of study. By using ANOVA (analysis of variance) test, we detected a significant difference(p=0.0001 for both) between means in the three groups of MWAp and HZ at presentation and at time of study. MWAp is significantly lower in G2 at presentation (94.77+/-11.29 % vs 104.86+/-10.96 in G1 and 111.53+/-16.63 % in G3) and at time of study (97.51+/-12.96% vs 104.72+/-14.04% in G1 and 113.44+/-15.62% in G3). The same applies for HZ where G2 children had significantly lower values than other groups at presentation (-1.142+/-0.83 vs0.163± 0.906 in G1 and 0.541 ± 0.71 in G3) and at time of study(-0.202 ± 1.03 vs 0.064 ± 0.77 in G1 and 0.72 ± 0.796 in G3). However, no significant difference was found between groups concerning IBWp neither at presentation nor at time of study.

Table 1. Socio-demographic characteristics of recruited children

Parameters		G1	G2	G3	p-value
Sex	**Male**	**(5) 13.9**	**(14) 33.3**	**(10) 29.4**	**0.12**
	Female	(31) 86.1	(28) 66.7	(24) 70.6	
Consanguinity	Yes	(6)18.2	(10)27	(9)26.5	0.682
	No	(27)81.8	(27)73	(25)73.5	
Age at presentation	<ou = 2years old	(18)50	(28)68.3	(25)73.5	0.094
	> 2 years old	(18)50	(13)31.7	(9)26.5	

Table 2. Characteristics at birth of recruited children

Parameters		G1	G2	G3	p-value
Birth term	On term	(33) 91.7	(37) 88.1	(31) 91.2	0.854
	Premature	(3) 8.3	(5) 11.9	(3)8.8	
Delivery mode	Vaginal delivery	(16)44.4	(16)38.1	(17)50	0.604
	C-Section	(20)55.6	(26)61.9	(17)50	
Length at birth (cm)		49.75 ± 5.965	48.62+/-2.56	50.2 ± 2.68	0.204
Weight at birth(Kg)		3.10 ± 0.81	3.27 ± 1.47	3.14 ± 0.836	0.931

Table 3. Previous episodes of urinary tract infection

Parameter		G1 + G2	G3	p-value
Previous history of urinary tract infection	No	41.1%(32)	64.7%(22)	0.0357*
	Yes	58.9%(46)	35.3%(12)	

Table 4. Results of urine culture in recruited children

Parameters		G1	G2	G3	p-value
Organism	E.Coli	(26)72.2	(38)90.5	(31)91.2	0.266
	Proteus	(6)16.7	(2)4.8	(2)5.9	
	Klebsiella	(3)8.3	(2)4.8	(1)2.9	
	Cytrobacter	(1)2.8	0	0	
ESBL	Yes	(7)19.4	(34)81	(7)20.6	0.0001*
	No	(29)80.6	(8)19	(27)79.4	

Table 5. Growth indices in three groups at presentation and at time of study

Parameters	G1	G2	G3	p-value
MWAp at presentation (%)	104.86 ± 10.96	94.77 ± 11.29	111.53 ± 16.63	0.0001*
HZ at presentation	0.163± 0.906	-1.1452 ± 0.83	0.541 ± 0.71	0.0001*
MWAp at time of study (%)	104.72 ± 14.04	97.51 ± 12.96	113.44 ± 15.62	0.0001*
HZ at time of study	0.064 ± 0.77	-0.202 ± 1.03	0.72 ± 0.796	0.0001*
IBWp at presentation (%)	101.58 ± 14.4	103.21 ± 12.14	101.5 ± 13.77	0.815
IBWpat time of study (%)	96.14 ± 25.92	101.1 ± 19.55	101.8 ± 9.57	0.410
Follow up duration (years)	5.85 ± 3.11	5.71 ± 3.23	7.03 ± 2.209	0.116

Table 6. Association between laterality of VUR and growth indices

Growth indices	Unilateral G1(n=25)+G2(n=25)	Bilateral G1(n=11) +G2(n=17)	p-value
MWAp at presentation (%)	100.13 ± 11.09	97.74 ± 14.087	0.415
HZ at presentation	-0.6080 ± 0.978	-0.46 ± 1.266	0.578
MWAp at time of study (%)	101.14 ± 14.25	99.88 ± 13.52	0.715
HZ at time of study	-0.066 ± 0.931	-0.123 ± 0.94	0.807
IBWp at presentation (%)	102.62 ± 13.34	102.15 ± 13.35	0.883
IBWp at time of study (%)	99.5 ± 22.9	97 ± 22.74	0.649

Table 7. Evolution of HZ score following different modalities of treatment

	HZ at presentation	HZ at time of study	p- value
Antibiotic prophylaxis G1 (n=24)	0.075+/-0.994	-0.013+/-0.759	0.724
Surgical treatment G1 + G2 (n=2) + n=26)	-1.269+/-0.921	-0.182+/-0.995	<0.001*
Antibiotic prophylaxis G2 (n=12)	-0.6+/-0.566	-0.167+/-1.159	0.186

Table 8. Evolution of IBWp score following different modalities of treatment

	IBWp at presentation	IBWp at time of study	p-value
Antibiotic G1	99.33+/-12.257	101.625+/-11.224	0.338
Surgery G1+G2	102.93+/-12.936	104.138+/-11.65	0.632
Antibiotic G2	99.91 +/-7.103	100.58 +/- 11.532	0.878

Table 9. Evolution of MWAp score following different modalities of treatment

	MWAp at presentation	MWAp at time of study	p-value
Antibiotic G1	103.875+/-11.863	105.958+/-15.301	0.606
Surgery G1+G2	92.928+/-12.023	100.357+/-11.593	0.0168*
Antibiotic G2	97.912 +/- 9.13	91.917+/-9.529	0.108

On the other hand, Table 6 shows no statistically significant difference between growth indices and laterality of VUR (using student t test).

Evolution of growth indices

Tables 7,8 and 9 shows the evolution of growth indices between presentation and time of study regarding to modality of treatment used (antibiotic prophylaxis and surgical treatment) based on paired t test. We noticed a significant improvement in HZ and in MWAp in children who received surgical treatment (p=0.001) and (p=0.0168) respectively.

However, no significant increase was recorded in HZ and MWAp in children who received antibiotic prophylaxis in G1 and in G2 (Tables 7 and 9). Also, no significant change was detected in IBWp neither in children who received surgical treatmnent nor who received antibiotic prophylaxis (Table 8)

DISCUSSION

To begin with, percentage of girls in the three groups was higher than percentages of males. The same applies for the study of *Majid al Maliki et al.* (2011) done in Iran and published in 2011.

Whereas, in the study done by *Lin Shien* Fu et al. in China in 2009, the percentage of males in the study is higher. This can be attributed to elevated rate of circumcision in Lebanon and in Iran compared to China. Hence, uncircumcised children in China are more likely to present with febrile urinary tract infection that will reveal underlying VUR. For length and weight at birth, we note that they were in normal ranges even in G2. This is because antenatal growth depends on three factors: maternal, fetal and placental factors. So, VUR effect on growth will not be significant at birth. Concerning percentages of ESBL infection, we saw that the highest percentage was in G2, which means that a moderate to severe VUR predisposes to ESBL infection probably due to repetitive infection and continuous use of antibiotics.

Then, concerning growth indices, we are going to analyse each one alone:

- **HZ score:** Children in G2 had significantly lower HZ than other groups. This difference was also found in *Keskinoglu et al.* 2017) published in 2014 , but was not detected in *Boquedano et al.* (2000). The latter study had a smaller sample size: 34 children with VUR while we had 78 children with VUR.
- **IBWp:** In our study, we didn't find a significant difference in IBWp between the 3 groups. Also, non significant results were obtained in *Majid Maliki et al.* and *Boquedano et al.*
- **MWAp:** In our study, we had significantly lower values in children in G2. This indice that we have created may resemble weight z score used in *Keskinoglu et al* and which was also significantly lower in children with VUR.

To explain the decrease of MWAp and HZ score in children in G2, let's find some hypothesis:

The first hypothesis is secretion of endogen steroids in response to stress caused by infection. Hence, the high level of steroids will inhibit the secretion of growth hormone. The second hypothesis is that renal scars caused by repetitive urinary tract infection is likely to cause a decrease in IGF secondary to an increase of IGF binding protein. This theory was suggested *Sankar Kumas Dal et al.* (2010) published in 2010. In the latter study, IGF was decreased in children with VUR with a renal clearance (>50mL/min), whereas growth hormone was elevated. In our study, this theory can be neither confirmed nor rejected because renal function of children wasn't monitored via dosing of serum creatinine during follow up period and renal scintigraphy wasn't done also. The third hypothesis suggests a transient pseudohypoalsdosteronism secondary to VUR. This theory was proposed by a case report published by *Klingenberg et al*. (2006) regarding a child who was admitted for poor growth and was found to have pseudohypoaldosteronism secondary to VUR. But this hypothesis may be excluded because any of children in our study presented with hyponatremia or hyperkalemia. Last but not least, concerning treatment modalities, we found a significant improvement in HZ and MWAp in children who received surgical treatment , same as *Polito et al*. (1997) et *Merell et al.* (1979) in 2005. However, in children who received antibiotic prophylaxis, no significant growth indices improvement was found. In study of *Guidos et al.* (2017). in United States in 2017, they detected a decrease in percentile of height in children who received antibiotic prophylaxis.

Limitations

Our study is unicentric which means that we need a larger and more representative sample, so we will be able to generalize our results. Moreover, we classified children according to voiding cystourethrogram results. But, sometimes we may have a normal voiding cystourethrogram despite the presence of VUR (Traubici Jeffrey, 2008), which causes a wrong classification of children with VUR in the control group (G3). Also, renal function of children was not monitored and IGF and GH level were never measured, so we cannot know the exact mechanism of decrease of growth indices in children with VUR.

Conclusion

To sum up, our study showed a normal length and weight in children with vesico-ureteral reflux atbirth and a decrease of HZ and MWAp in children with moderate to severe VUR at presentation and at time of study and surgical treatment appears to improve these indices. However, a larger sample may be needed to be able to generalize , and also a measure of IGF and Growth hormone in chidren with VUR maybe interesting to determine the exact mechanism of decreased HZ and MWAp compared to normal children.

Acknowledgments

We would like to thank the archive unit in Notre Dame des secours university hospital in Byblos. We note that no funding was received from any source.

Authors contributions : Georges Nicolas planned the study design and Roula Hneinehdid the data collection and analysis, and bothauthors contributed to writing and revising of this manusript.

Conflict of interest : The authors declare no conflict of interest.

Ethical considerations : Study was approved by ethical committee of the institution on August 2017.

Source of funding : The authors declare no source of funding

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