Open Access Review

Journal of Renal Endocrinology

J Renal Endocrinol 2018;4:e17.
http://www.jrenendo.com

Nickan Research Institute

Thromboembolism due to nephrotic syndrome among children; a systematic review and meta-analysis

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Abstract
The importance of nephrotic syndrome among children is mostly due to its related life-threatening events such as thromboembolic events. The present review attempted to systematically assess the pooled prevalence of thromboembolism in nephrotic syndrome among children. This study was performed according to established methods and in compliance with PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis) Protocols. Two investigators searched Medline, Web of Knowledge, Google Scholar, Scopus, and Cochrane databases for all eligible studies in accordance with the considered keywords including "thromboembolism", "nephrotic syndrome", and "child". Of total 99 studies that initially assessed based on the keywords published, 11 met the endpoints (published from 1973 to 2012) that were finally analyzed. The data of 5085 children who suffered nephrotic syndrome were assessed. The number of patients in the studies ranged 26 to 3377. The pooled prevalence of thromboembolic events due to nephrotic syndrome among children was estimated to be 6.0% (95% CI: 3.0% to 11.4%). The heterogeneity was high with an I2 of 92.73% ($P<0.001$) for assessing the pooled prevalence of thromboembolic events in infantile nephrotic syndrome with the stud-related weight ranged 1.40% to 43.08%. There was a significant publication bias as evidenced by either funnel plot asymmetry or Egger test ($P=0.156$). The overall prevalence of nephrotic syndrome nephrotic syndrome children widely ranges 1.40% to 43.08%, however high heterogeneity obtained by reviewing the literature emphasizes the necessity for further assessment of this event among children from the point of view of etiological and pathophysiological basis.
Keywords: Nephrotic syndrome, Thromboembolism, Children, Thromboembolic events
Citation: Tahouri T, Nazari S, Sheikhvatan M. Thromboembolism due to nephrotic syndrome among children; a systematic review and meta-analysis. J Renal Endocrinol. 2018;4:e17.

Introduction

Infantile nephrotic syndrome is a common kidney disorder with an overall incidence of 2 to 7 per 1000 with the prevalence of 16 per 1000 children (1,2). The importance of this phenomenon among children is mostly due to its related life-threatening events such as infections, kidney progressive dysfunction, drug-induced side effects, and thromboembolic events (3-5). Although venous thromboembolism is a rare complication of nephrotic syndrome, the devastating nature of thromboembolism has been also reported among children leading considerable mortality and morbidity because of the concurrent serious clinical conditions such as cardiovascular disorders, malignancies, end-stage renal disease, and cerebrovascular accidents (6-8). Due to these conditions, the increased likelihood of early and long-term death in children with venous thromboembolism following nephrotic syndrome is potentially expected. While the main pathophysiology of nephrotic syndrome among children remains obscure, it seems to be multifactorial. Like to other clinical syndromes, the genomic background even unrelated to underlying renal disease has a major role in occurring venous thromboembolism in such children (9,10). Besides, it has been suggested that losing proteins can alter coagulation regulatory proteins that leads to an increased hypercoagulable tendency in vessels (11,12). However, several subjects have been questioned regarding venous thromboembolism due to the infantile nephrotic syndrome. First, the spectrum of the prevalence of this event among children is very wide and it has not already reached a global consensus. Second, the evidence to support the probable pathophysiological fundaments of this complications is somewhat lacking needing further assessment. Hence, the present review attempted to systematically assess the pooled prevalence of thromboembolism in nephrotic syndrome among children.

Materials and Methods

Search strategy

This study was performed according to established methods and in compliance with PRISMA-P (Preferred

Received: 10 November 2017, Accepted: 14 January 2018, ePublished: 14 February 2018

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Implication for health policy/practice/research/ medical education

It should be noted that the occurrence of thromboembolism following nephrotic syndrome has a multifactorial nature so along with genetic predisposition, other conditions including inflammation, central venous catheters, coagulopathies, and even medications can increase the likelihood of thromboembolism in such patients.

Reporting Items for Systematic review and Meta-Analysis) Protocols (13). Two investigators searched Medline, Web of knowledge, Google Scholar, Scopus, and Cochrane databases for all eligible studies in accordance with the considered keywords including "thromboembolism", "nephrotic syndrome", and "child". The studies were restricted to the English language. The inclusion criterion for retrieved the studies was venous thromboembolism in infantile nephrotic syndrome. The exclusion criteria were thus as follows: 1) a lack of clear and reproducible results, 2) non-English studies, 3) lack of access to the manuscripts full texts, and 4) case reports, case series and review paper.

Data abstraction and validity assessment

Data abstraction was independently performed by two blinded reviewers on structure collection forms without divergences in data collection. The study quality was evaluated based on the following criteria; 1) the systematic review and meta-analysis based on the questions primarily described and formulated; 2) inclusion and exclusion criteria predefined in the studies as eligibility criteria; 3) searching the literature performed on a systematic and comprehensive approach; 4) to minimize the bias, the full texts of the article were dually reviewed; 5) the quality of included studies were rated independently by the reviewers for appraising internal validity; 6) studies' characteristics and findings were comprehensively listed; 7) the publication and risk of bias were listed; and 8) heterogeneity was also assessed (13). The present study intended to determine prevalence and main correlates of thromboembolism in nephrotic syndrome among children. Along with this endpoint, the year of publishing, number of patients included, the method of design, and the tools employed for assessing thromboembolism events were also pointed. Of total 99 studies that initially assessed based on the keywords published between 1957 and 2017, 11 met the endpoints (published from 1973 to 2012) that were finally analyzed (15-25).

Statistical analysis

Dichotomous variables are reported as proportions and percentages, and continuous variables as mean values. Binary outcomes from individual studies were to be combined with both the Mantel-Hansel fixed effect model. The odds ratio (OR) and 95% confidence interval (CI) were used as summary statistics for the comparison of dichotomous variables between the radial and femoral approach. Cochran's Q test was used to determine the statistical heterogeneity of this study. This test was complemented with the I^2 statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0%–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and 76%–100% high heterogeneity. Publication bias was assessed by the rank correlation test and also confirmed by the funnel plot analysis. Reported values were two-tailed, and hypothesis testing results were considered statistically significant at $P = 0.05$. Statistical analysis was performed using the Stata software (version 13.1, Stata Corp, College Station, TX, USA).

Results

As summarized in Table 1, in total, 11 papers were systematically reviewed (15-25). Of those, 9 studies were retrospectively planned and only two studies were performed prospectively. The manuscripts were published from 1973 to 2012. Totally, the data of 5085 children who suffered nephrotic syndrome were assessed. The number of patients in the studies ranged 26 to 3377. Based on the meta-analysis, the pooled prevalence of thromboembolic events due to nephrotic syndrome among children was estimated to be 6.0% (95% CI: 3.0% to 11.4%). In seven studies (15-22), only symptomatic thromboembolism was reports, in two studies (16-23) congenital thromboembolism was described, in one study (24), in addition to explaining symptomatic thromboembolism, the secondary causes of this event were also described and only in the recent study (25), the evidence of thromboembolism obtained by Dual Energy CT Angiogram was described that all subjects were asymptomatic at time of imaging. The statistical heterogeneity was considerably high with an I^2 of 92.73% ($P<0.001$) for the assessing pooled prevalence of thromboembolic events in the infantile nephrotic syndrome with the stud-related weight ranged 1.40% to 43.08% (Table 2) (Figure 1). There was a significant publication bias as evidenced by either funnel plot

Table 1. The details of the studies reviewed for thromboembolism in childhood nephrotic syndrome

Author, year	Study type	Number	TE event	Prevalence
Egli, 1973	Retrospective	3377	60	1.8
Mahan, 1984	Retrospective	41	4	9.8
Hoyer, 1986	Retrospective	26	7	26.9
Mehls, 1987	Retrospective	204	9	4.4
Tsau, 1991	Retrospective	193	2	1.0
Schlegel, 1997	Retrospective	360	11	3.0
Citak, 2000	Prospective	49	2	4.1
Lilova, 2000	Retrospective	447	9	2.0
Hamed, 2001	Retrospective	30	4	13.0
Kerlin, 2009	Retrospective	326	30	9.2
Zhang, 2012	Prospective	32	9	28.1
Total		5085	150	2.9

Table 2. The details of calculating pooled prevalence of thromboembolism in nephrotic syndrome among children

Author, year	Event rate	Lower limit	Upper limit	Z value	*P* value	Weight
Egli, 1973	0.018	0.014	0.023	-30.803	<0.001	43.08
Mahan, 1984	0.098	0.037	0.233	-4.277	<0.001	2.64
Hoyer, 1986	0.269	0.134	0.467	-2.258	0.024	3.74
Mehls, 1987	0.044	0.023	0.083	-9.021	<0.001	6.29
Tsau, 1991	0.010	0.003	0.040	-6.414	<0.001	1.45
Schlegel, 1997	0.031	0.017	0.054	-11.290	<0.001	7.79
Citak, 2000	0.041	0.010	0.149	-4.373	<0.001	1.40
Lilova, 2000	0.020	0.011	0.038	-11.537	<0.001	6.45
Hamed, 2001	0.133	0.051	0.306	-3.485	<0.001	2.53
Kerlin, 2009	0.092	0.065	0.129	-11.947	<0.001	19.91
Zhang, 2012	0.281	0.153	0.458	-2.386	0.017	4.73
Fixed	0.039	0.033	0.046	-37.377	<0.001	---
Random	0.060	0.030	0.114	-7.661	<0.001	---

I square = 92.731, $P < 0.001$

asymmetry or Egger test ($P = 0.156$) (Figure 2).

Discussion

Thromboembolism due to nephrotic syndrome has a wide different epidemiological aspect in children and adults with high overall prevalence in adults (about 25%) as compared with children to be approximately 3%. Additionally, the pattern of this event is widely varied as primary and secondary, congenital and acquired, as well as with and without genetic basis. The overall prevalence of thromboembolism in nephrotic syndrome varies with the type of nephrotic syndrome dependent on different factors. First, the prevalence of thromboembolism is significantly different in children with congenital nephrotic syndrome as compared to those with secondary nephrotic syndrome due to inflammatory (vasculitis) or infectious (viral) causes (23-25). In our systematic review, the prevalence of thromboembolism due to congenital nephrotic syndrome ranged 9.8% to 13.0%, while in secondary nephrotic syndrome widely ranged from 1.8% to 28.1%. Age is a major factor for explaining the pathophysiological fundament of thromboembolism due to nephrotic syndrome. In adults, the main factor predisposing the occurrence of thromboembolism in the background of nephrotic syndrome is renal vein thrombosis that its likelihood seems to increase with advancing age. In children, about 10% of thromboembolisms occur congenitally, while the risk of thromboembolism due to nephrotic syndrome positively increases by advancing age from the relative risk of 1.16 in early childhood to 8.59 in those aged >12 years (26-28). Another important factor affecting the incidence of thromboembolism in infantile nephrotic syndrome is the time interval between nephrotic syndrome and first thromboembolic event. It has been shown that about 61% of thromboembolism events during childhood occur within three months after diagnosis of nephrotic syndrome (29). Besides the patients-related factors, the potential limitations of the studies such as retrospectively or prospectively designing of the study, the study power due to employed sample

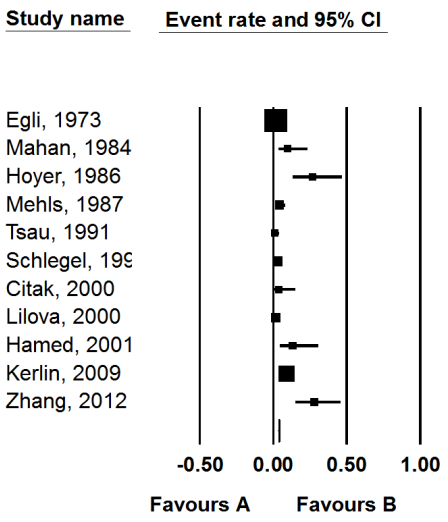

Figure 1. The statistical schema for assessing pooled prevalence of thromboembolic events in infantile nephrotic syndrome.

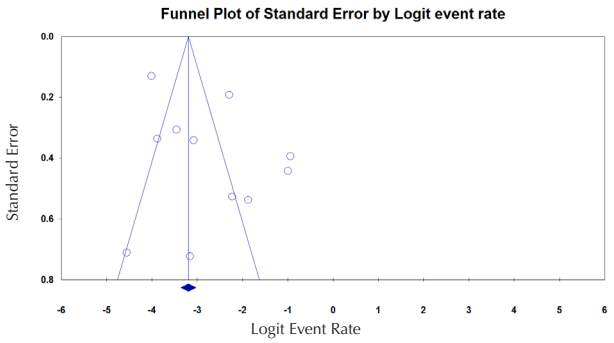

Figure 2. Significant publication bias as evidenced by either funnel plot asymmetry.

size, thromboembolism definitions, baseline renal histopathology, and the presence of imaging evidence can influence the incidence rate of thromboembolic events due to nephrotic syndrome within childhood. As indicated well in our review, most results were obtained

from the studies with retrospective approaches that might be potentially affected by data collection biases. Also, only one study used imaging modalities for assessment and confirming thromboembolism. More important, sample sizes included in the studies widely varied leading different study weighting and thus considerable heterogeneity. Additionally, the pathophysiology of thromboembolism in the background of nephrotic syndrome has not been clearly understood. A few studies focused the genetic and inherit basis of this event especially among children. Based on our reviewing the literature, only four studies pointed the genetic aspects of this event among children (30-33). As shown by Suri et al (30), the coexistence of genetic pro-thrombotic conditions might have a major role in the likelihood of thromboembolism in nephrotic syndrome. Fluss et al (31) believed that inherited thrombophilia was the main basis for appearing thromboembolism is some nephrotic syndrome children. As shown by Eddy et al (32), some mutations in the genes encode podocyte proteins might involve in thromboembolism and finally Schlegel et al (33) believed that any mutation in the gene encoding the factor V Leiden might a role in predisposing thromboembolism.

Conclusion

It should be noted that the occurrence of thromboembolism following nephrotic syndrome has a multifactorial nature so along with genetic predisposition, other conditions including inflammation, central venous catheters, coagulopathies, and even medications can increase the likelihood of thromboembolism in such patients (34,35). However, both epidemiological and pathophysiological aspects of thromboembolism in childhood nephrotic syndrome have studied very little and should be evaluated with a greater scope with employing both clinical, molecular and imaging tools.

Acknowledgments

The authors wish to thank Clinical Research Development Center of Rasoul-e-Akram hospital, Iran University of Medical Sciences for technically supported implementation of the project.

Authors' contribution

All authors contributed equally to the manuscript.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

Conflicts of interest

The authors declare that they have no conflict of interest.

Funding/Support

None.

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