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ORIGINAL ARTICLE

Urinary nerve growth factor: a biomarker for detrusor overactivity in children? A meta-analysis and trail sequential analysis

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Abstract

Purpose Based on, previously, a systematic review, urinary nerve growth factor (NGF) has emerged as one potentially noninvasive biomarker for detrusor overactivity (DO) in adults. We performed this systematic review to explore if NGF is a biomarker for DO in children.

Methods A literature search was conducted in PubMed, Embase, Web of science, and Cochrane Library. Copies of all relevant articles were retrieved for quality assessment and data abstraction by two reviewers. Primary outcome was pooled standardized mean difference (SMD) for NGF/Cr (NGF normalized to urine creatinine) level between DO group and controls.

Results Three case–control studies published from 2012 to 2016 were included with 74 patients and 70 controls. Children with DO had a significant higher baseline urinary NGF/Cr level compared to controls (SMD = 2.48, 95%CI = 0.85–4.10, $P < 0.01$). After treatment, the level of NGF/Cr decreased significantly compared to baseline level at 6th month time points (SMD = 0.94, 95%CI = 0.03–1.86, $P = 0.04$). We calculated the required information size to 99 patients for comparison of urinary NGF/Cr level between DO and controls by trail sequential analysis (TSA).

Conclusion Based on this systematic review, NGF/Cr may be a noninvasive biomarker for DO in children in the future. However, based on TSA, more original studies are needed to clarify the role of NGF/Cr in the biomarker effect.

Keywords Biomarker · Children · Detrusor overactivity · Systematic review · Trail sequential analysis · Urinary nerve growth factor

Introduction

Overactive bladder (OAB) is defined by the International Children's Continence Society (ICCS) as urinary urgency, usually accompanied by frequency and nocturia, with or without urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology [1, 2]. OAB can only be diagnosed after a child is toilet trained and has reached at least 5 years of age, but if a child is toilet trained before the age of 5, they can have OAB [1–3]. OAB is reported from all over the world, with a prevalence of 5–12% in children and a prevalence of 0.5% in older adolescents [3]. Published data indicate that around one-third of children with OAB are likely to become adults with similar complaints [3–5]. Children with OAB usually have detrusor overactivity (DO), but this label can only be applied with cystometric evaluation [1–3]. Furthermore, urodynamics is an invasive investigation with a risk of urinary tract infections.

Therefore, urodynamics is not a perfect biomarker for DO. In the search for a reliable, noninvasive alternative to urodynamics, much interest has focused on NGF [6, 7]. A growing number of studies confirmed a positive correlation between enhanced NGF and adult with OAB or DO [8–12]. Meanwhile, based on, previously, a systematic review, NGF has emerged as one potentially noninvasive biomarker for DO in adults, although the data are imprecise and, hence,

Wei Zhang and Changkai Deng have contributed equally to this work.

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cannot be recommended for use in the current clinical practice [13, 14]. We performed this systematic review to explore if NGF is a biomarker for DO in children.

Methods

Publication search

Four databases (PubMed, Embase, Cochrance Library, and Web of Science) were electronically searched to retrieve studies by October 2018. The search terms were: ('Detrusor overactivity' OR 'DO') AND ('Nerve growth factor' OR 'NGF'). In addition, we evaluated all the associated publications and their reference lists to identify the most eligible literature. This systematic review was based on the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines [15].

Inclusion and exclusion criteria

The studies were considered in this meta-analysis if they met all of the following criteria: (1) the study explored the relationship between urinary NGF/Cr level and DO only under 18 years old; (2) all patients were diagnosed with DO; (3) available data provided or could be calculated from the other information; (4) if multiple publications reported on overlapping data or the same, the article based on the largest study population or the most recent article was included; (5) the publication language was English. Studies were excluded if they met any of the following criteria: (1) provided only the data of urine NGF without NGF/Cr; (2) published only as abstracts, reviews, commentaries, or editorials; (3) articles with incomplete or useless data.

Data extraction

Two authors reviewed all eligible publications independently based on the inclusion and exclusion criteria. Then, we extracted the relevant data in accordance with data extraction form. Disagreements were solved by discussion or the third author was involved when necessary. The following information was extracted from each article: first author, publication date, geographical region, sample size of case and control groups, age, study design, measured method, and urinary NGF/Cr level.

Quality score assessment

The quality of studies was assessed by two authors according to the Newcastle–Ottawa Scale [16]. The study can be awarded one star for each item, except for comparability awarded two stars. The study which awarded seven or more stars was graded as high quality.

Statistical analyses

The standard mean difference (SMD) and 95%CI were calculated using Review Manager Version 5.2 software. Heterogeneity among included studies was checked by Q test and I^2 test. If the data showed no heterogeneity ($P > 0.05$, $I^2 < 50\%$), fixed effect model was used; otherwise, random-effect model was used. Sensitivity analysis was performed with Stata 12.0. Publication bias was evaluated by Egger linear regression test. Subgroup analyses were not conducted for only three original studies included. The threshold for statistical significance was adjusted by trail sequential analysis (an overall 5% risk of a type I error and 20% of the type II error) when original studies are sparse [17–19].

Results

Literature selection and study characteristics

The detailed process of literature selection is presented in Fig. 1.The general characteristics of included studies are presented in Table 1. There were three published case–control studies (74 patients, 70 controls) included in our meta-analysis from 2012 to 2016 [20, 21, 23]. The scores of study quality, evaluated by the Newcastle–Ottawa Scale (NOS), ranged from 4 to 5 (Table 2).

Meta-analysis results

Comparison of urinary NGF/Cr level between DO and controls

Compared with controls, DO children presented significantly higher urinary NGF/Cr level (SMD = 2.48, 95%CI = 0.85–4.10, $P < 0.01$). There was statistically significant heterogeneity among included studies ($I^2 = 92\%$, $P < 0.01$) (Fig. 2; Table 3).

Comparison of urinary NGF/Cr level between pre-treatment and post-treatment (6th month)

Compared with post-treatment (6th month), DO children presented significantly higher urinary NGF/Cr level (SMD = 0.94, 95%CI = 0.03–1.86, $P = 0.04$). There was statistically significant heterogeneity among included studies ($I^2 = 78\%$, $P = 0.04$) (Table 3). For details, see the supplementary materials (Fig. S1).

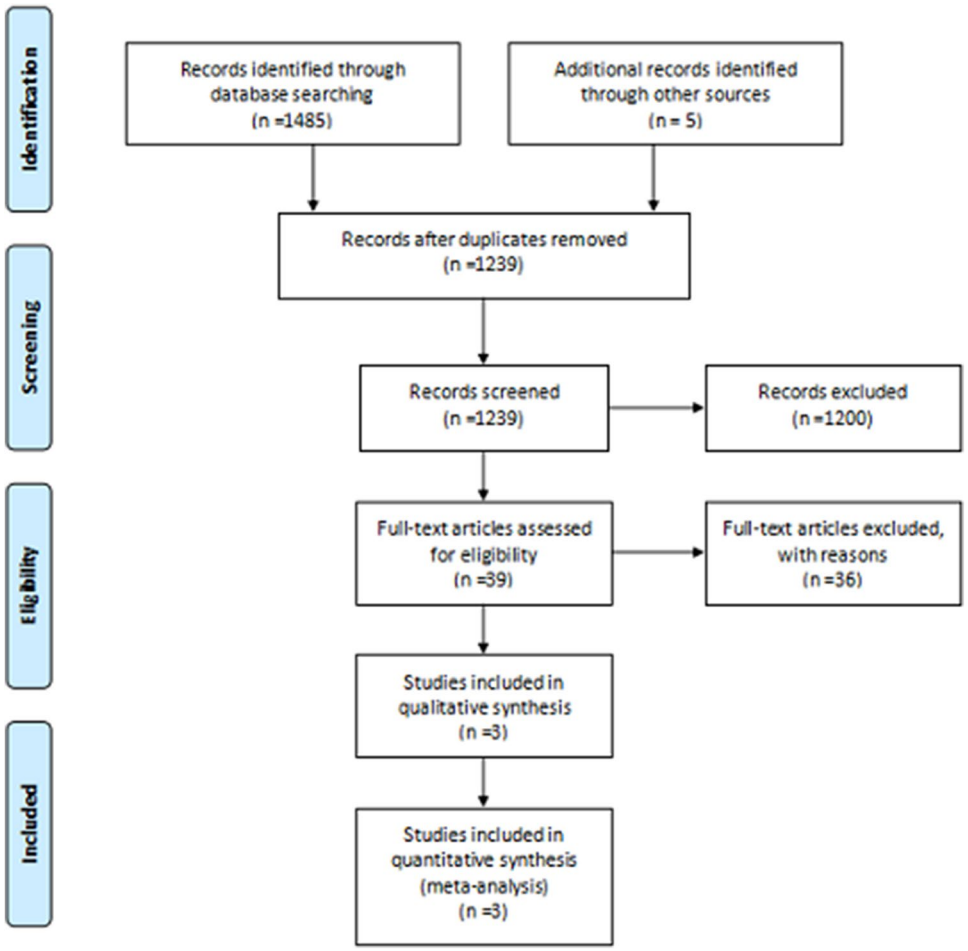

Fig. 1 Flowchart of literature selection

Table 1 Characteristic of the studies included in meta-analysis of association between urinary NGF/Cr and DO

Study	Location	Number/intervention	Study design	Age (DO/control)	Measured method	Followed (months)	Outcome
Ozdemir [21]	Turkey	OAB ($n=24$) Control ($n=30$)	Case–control	8.25 (1.5–17) years 11 (3–17) years	Enzyme-linked immunosorbent assay	6	NGF/Cr
Korzeniecka-Kozerska [22]	Poland	OAB ($n=24$) Control ($n=20$)	Case–control	109.7 ± 31.8 (months) 110.7 ± 31.9 (months)	Enzyme-linked immunosorbent assay	4–6	NGF/Cr
Oktar [20]	Turkey	DO ($n=26$) Control ($n=20$)	Case–control	NA 8.1 ± 1.65 (years)	Enzyme-linked immunosorbent assay	6	NGF/Cr

Sensitivity analysis

The results of our study were reliable and stable. For details, see the supplementary materials (Figs. S2, S3).

Publication bias

The results of Egger's linear regression test supported the conclusion of no significant publication bias ($P_{\text{Egger}}=0.104$) (see Table 3).

Trail sequential analysis

We calculated the required information size to 99 patients for comparison of urinary NGF/Cr level between DO and controls, and found that NGF/Cr level as a biomarker turned out to be false positive (Fig. S4). We calculated the required information size to 1866 patients for the comparison of urinary NGF/Cr level between pre-treatment and post-treatment (6th month), and found that NGF/Cr level as a biomarker turned out to be no statistical significance (Fig. S5).

Table 2 Quality assessment of the included studies

Study	Selection				Comparability	Exposure			Total no. of star
	Definition of cases	Representative of cases	Selection of cases	Definition of controls		Ascertainment of exposure	Method of ascertainment	Non-response rate	
Ozdemir [21]	*	–	–	*	*–	–	*	–	4
Korzeniecka-Kozerska [22]	*	*	–	*	*–	–	*	–	5
Oktar [20]	*	–	–	*	*–	–	*	–	4

* The study be awarded one star for each item

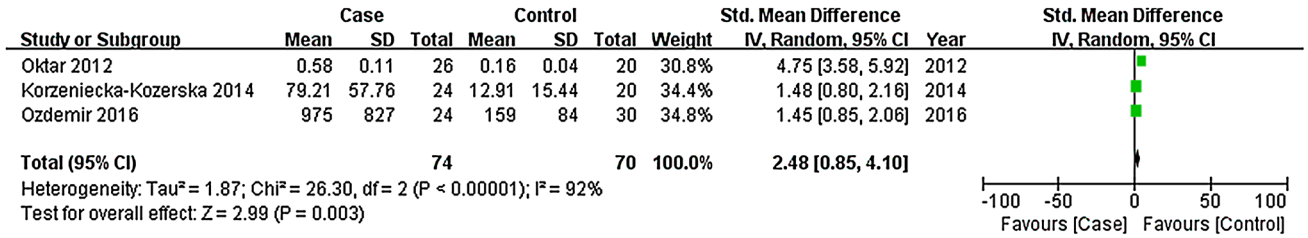

Fig. 2 Forest plots of comparison of urinary NGF/Cr level between DO and controls

Table 3 Results of the meta-analysis and publication bias

Study	Pooled SMD (95%CI)	Heterogeneity			Egger's test	
		P	I^2 (%)	*P*	*t*	*P*
Case vs. control	2.48 (0.85, 4.10)	0.003	92	< 0.01	6.09	0.104
Pre-treatment vs. post-treatment (6th month)	0.94 (0.03, 1.86)	0.04	78	0.03	–	–

Discussion

At present, objective assessment of DO has traditionally been made by cystometric study with the aim to reproduce urgency [3, 7, 25], but a dearth of evidence for benefit of cystometry is over OAB Symptom Score (OABSS) for patients with urgency and repeated cystometry is unacceptable to children [3, 25]. A more objective method to diagnose and predict prognosis in DO patients, especially for health care providers not trained in urology, needs to be found [3]. More and more interest has focused on neurotrophins, especially NGF [13, 14, 26], which have been implicated in the neuromodulation of micturition pathway plasticity associated with DO [27]. Some studies reported that urinary NGF or NGF/Cr level was significantly increased in patients with DO compared with controls and accorded with another systematic review [11, 13, 14]. Rachaneni et al. [13] performed a systematic review based on the eight articles which found that urinary NGF or NGF/Cr was increased in DO in adults. Based on the previous studies, NGF has emerged as one potentially non-invasive biomarker for DO in adults, although it is lack of sensitivity and specificity [13, 14, 28–30]. However, only a little studies have focused on the association between NGF level and DO in children [20, 23, 31]. To overcome the limitation of individual studies, we performed this systematic review to explore whether NGF is a biomarker for DO in children or not.

We included three original studies in our meta-analysis to explore the association between urinary NGF/Cr level and children with DO. Our analysis indicated that children with DO had a significant higher baseline urinary NGF/Cr level than healthy controls (SMD = 2.48, 95%CI = 0.85–4.10, $P < 0.01$). Our results accorded with Korzeniecka–Kozerska's and Ozdemir's studies, which reported that NGF/Cr was significantly higher in the children with DO than in the controls, and illustrated that NGF/Cr may be a potential role as an objective biomarker for DO diagnosis [20]. Meanwhile, it was decreased

significantly compared to baseline level at 6th month time point (SMD = 0.94, 95%CI = 0.03–1.86, $P = 0.04$). It was indicated that NGF/Cr can be used as a biomarker for monitoring the therapeutic outcome in children with DO. As Oktar et al. [20] concluded that NGF/Cr could not only be a potential biomarker for children with DO, but also a predictor of therapeutic efficacy in children with DO [23]. Therefore, based on our meta-analysis, it was suggested that NGF/Cr might have a potential to be a biomarker for diagnosis and evaluation of DO.

Because of only three original studies and repetitive testing of accumulating data, the meta-analyses are at risk of producing random errors and should not be trusted without TSA [17, 18]. Therefore, we adjusted the meta-analysis with TSA that widened the confidence intervals if the data were too sparse to draw firm conclusions [17–19]. Based on TSA, the results indicated that NGF/Cr level as a biomarker turned out to be false positive. A systematic review of eight studies in adults demonstrated that NGF or NGF/Cr cannot be used as a biomarker for DO at present because of its lack of sensitivity and specificity [13]. Thus, more original studies are needed to clarify the role of NGF/Cr level in the biomarker effect for DO in children.

The results of our meta-analysis should be interpreted cautiously for several limitations. First, we searched possible studies in four databases. There may be some other relevant articles issued in other databases. Second, some relevant studies could not be included in our analysis because of incomplete raw data. Third, we could not explore the sources of heterogeneity among all studies for only three studies included. Fourth, our meta-analysis was based on case–control studies and the original studies were awarded four or five stars as low quality.

Conclusion

The results of this meta-analysis suggest that NGF/Cr may be a potential role as an objective biomarker for the diagnosis and evaluation of DO. However, based on TSA, more original studies are needed to clarify the role of NGF/Cr in the biomarker effect for DO in children.

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Compliance with ethical standards

Conflict of interest The authors have no relevant financial relationships to the article to disclose.

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