

Letter to the reviewer.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: In this research, authors reported different options for management of neurogenic bladder dysfunction in pediatric population. Here, management options were reported based on physiopathological mechanisms. Authors provided a well structured report with good language quality. Well done.

Dear reviewer #1

Thank you very much for your comments, we made some changes in the manuscript to improve the style, we are hoping that the corrected manuscript will fulfill the Journal style

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The article is within the scope of the journal. However, it cannot be accepted if some improvements are not made: a) In the abstract it is not clear what is the objective and the contribution of the article. b) The article is not well structured. A structure such as: Introduction, Materials, Methods, Results, Discussion and Conclusions should be used. c) The article has no cohesion in the presentation of the results. d) The style of the article should be improved. For example there are different line spacing. The text is not justified.

Dear reviewer #2:

Thank you very much for your comments and instruction which will improved the manuscript.

a) **In the abstract it is not clear what is the objective and the contribution of the article.**

Answer: 1-The abstract was reformulated to the objectives clear and paragraph was added to show the objectives. 2- The title is modified to express the aim of the work.

Lower urinary tract dysfunction in pediatrics progress to CKD in adolescents and young people: Personalized management

Abstract

Newborn infants who had neurogenic bladder dysfunction (NBD) have a normal upper urinary tract at . Most of them will develop deterioration of renal function and chronic kidney disease (CKD) in case they do not received proper management.

Renal damage is due to high detrusor pressures resulted from poor compliance of the bladder, beside detrusor overactivity against a closed sphincter or detrusor sphincter dyssynergia.

To preserve renal function and prevent deterioration of the kidneys, NBD must be treated immediately after being diagnosed. Over the last few years there were great progress in the treatment of children with the NBD. Neurogenic bladder dysfunction in children must be diagnosed early in life and the child should receive the proper management, neglecting the case or improper management would end with deleterious effect on the

upper tract that end with renal dysfunction and chronic kidney failure. There are different options for management. The type of management would be personalized for every case and could be changed accordingly.

Lower urinary tract dysfunction in pediatrics progress to CKD in adolescents : Personalized management with pharmacological, Interventional, and new modalities to prevent upper tract deterioration.

Abstract Newborn infants who had neurogenic bladder dysfunction (NBD) have a normal upper urinary tract at birth. Most of them will develop deterioration of renal function and chronic kidney disease (CKD) in case they do not received proper management. Children with NBD would develop renal damage at adolescence or earlier which is due to high detrusor pressures resulted from poor compliance of the bladder, beside detrusor overactivity against a closed sphincter or detrusor sphincter dyssynergia. To preserve renal function and prevent deterioration of the kidneys, NBD must be treated immediately after being diagnosed. Over the last few years there were great progress in the treatment of children with the NBD. We searched PubMed and the Cochrane Library for peer-reviewed articles published in any language up to March 10, 2021, using the search term “neurogenic bladder children”, our search excluded diagnosis, pathophysiology, surgical treatment of spinal cord injury, and spina bifida. The research identified the effectiveness of treatment regimens targeting prevention of chronic kidney disease (CKD), and the indications of kidney transplantation. Result of the research showed that NBD in children should be diagnosed early in life and the child should receive the proper management. The literature search concluded that the management of NBD in children would be personalized for every case and could be changed according to response to treatment, side effects, child compliance, availability of treatment modality, and costs of treatment. The objectives of the study are to present the different options of management of NBD in children and the selection of the proper method on a personalized manner.

- b) b) The article is not well structured. A structure such as: Introduction, Materials, Methods, Results, Discussion and Conclusions should be used.

Answer the article was re-structured to include introduction, material and methods, and conclusion, we deviated from the standard form of an original research article to be divided into 6 sections, to the format of review article which include introduction, material and methods, body of text, and conclusion, every sector in the body of the text included discussion.

Introduction

Newborn infants who had neurogenic bladder dysfunction (NBD) have a normal upper urinary tract at birth. Most of them will develop deterioration of renal function in case they do not received proper management (1, 2). Renal damage is due to high detrusor pressures resulted from poor compliance of the bladder, beside detrusor overactivity against a closed sphincter or detrusor sphincter dyssynergia (3,4). To preserve renal function and prevent deterioration of the kidneys, NBD must be treated immediately after being diagnosed. Over the last few years there were great progress in the treatment of children with the NBD. Neurogenic bladder dysfunction could be classified to subcategories according to urodynamic findings: A) Sphincter overactivity combined with a detrusor inactivity that result is incomplete bladder emptying. B) Sphincter overactivity during detrusor contraction that led to affection and deterioration of upper tract. C) incompetent sphincter associated with detrusor inactivity leading to large bladder capacity, urine leakage, and incomplete emptying. D) Detrusor hyperreflexia and loss of bladder compliance (5,6,7).

Introduction

Newborn infants who had neurogenic bladder dysfunction (NBD) have a normal upper urinary tract at birth. Most of them will develop deterioration of renal function in case they do not received proper management^[1,2]. Renal damage is due to high detrusor pressures resulted from poor compliance of the bladder, beside detrusor overactivity against a closed sphincter or detrusor sphincter dyssynergia^[3,4]. To preserve renal function and prevent deterioration of the kidneys, NBD must be treated immediately after being diagnosed. Over the last few years there were great progress in the treatment of children with the NBD. Neurogenic bladder dysfunction could be classified to subcategories according to urodynamic findings: A) Sphincter overactivity combined with a detrusor inactivity that result is incomplete bladder emptying. B) Sphincter overactivity during detrusor contraction that led to affection and deterioration of upper tract. C) incompetent sphincter associated with detrusor inactivity leading to large bladder capacity, urine leakage, and incomplete emptying. D) Detrusor hyperreflexia and loss of bladder compliance^[5-7]. Neglecting the case of neurogenic bladder dysfunction (NBD) or improper management would end with deleterious effect on the upper tract that end with renal dysfunction and chronic kidney failure. Since the introduction of clean intermittent catheterization (CIC) for the treatment of NBD, varieties of medication and intervention were introduced, children differ from adult in acceptance certain treatment modality, loss of compliance, and sensitivity to adverse effects. The variety of options made it possible to shift from one method to another seeking child acceptance, the aim is to avoid upper tract deterioration resulted from high pressure in the bladder. Objectives are to present different treatment options that has an FDA and EU approval for treatment of NBD in children. Each treatment modality has its advantage and limitations, consequently the management is to be personalized for every child.

Material and methods

We searched PubMed and the Cochrane Library for peer-reviewed articles published in any language up to March 10, 2021, using the search term “neurogenic bladder children” revealed 3,143 articles, 65 articles were fulfilling the criteria of the search. Articles that were excluded from the study were those dealing with diagnosis, urodynamic, pathophysiology, surgical treatment of spina bifida and spinal cord injury. The data collected ranged from standard methods of treatment of NBD to the newly introduced pharmacological product, minimally invasive interventions, and the place of kidney transplantation in cases of renal failure. The different modalities were classified to 1) standard initial management; 2) Pharmacological treatment; 3) Botulinum toxins; 4) Neural stimulation; 5) Vesicostomy; 6) kidney transplantation.

Every item presented for its mode of action, adverse effects, efficacy, availability, and factors influencing the choice of management. The data are presented in the narrative review.

Results

Innovations in the treatment of NBD in children had solved the dilemma of the ideal treatment, there are many options the would be used in treatment of NBD and guard against upper tract deterioration. Newly introduced drug delivery system using intravesical oxybutynin chloride solution supplemented with hydroxypropyl cellulose, which is a mucosal adhesive substance, reduced systemic side effects and proved to be safe and showed excellent efficacy [17, 18].

Drug delivery system using fluid suspension of the newly introduced antimuscarinics made it possible to treat pediatric population without the need for clean intermittent catheterisation, these drugs included: Solifenacin^[30,31], Tolterodine^[32], Propiverine^[33,34], Trospium^[35]. Studies demonstrated the superior tolerability of these drugs over oxybutynin, with higher efficacy and minimal side effects.

OnabotulinumtoxinA (Botox—BTX-A) intradetrusor injection has been proven to be an effective and safe long-term therapy for the management Neurogenic detrusor overactivity and NBD, it prevents incontinence, reflux and consequently deterioration of renal function. It can be repeated without causing fibrosis of detrusor muscle.

Neural stimulation with for children how are not compliant to CIC or refractory to pharmacologic approaches would benefit from percutaneous tibial nerve stimulation (PTNS). PTNS can modulate the voiding and storage function of the bladder leading to an overall subjective improvement of symptoms in about 60% of the patients and 47%–56% improvement of filling and voiding function parameters^[53-54]. Children with renal insufficiency due to NBD can receive a renal allograft and

achieve good long-term results. Correction of structural urogenital abnormalities and optimization of emptying and storage functions of the bladder has to be achieved before renal transplantation^[63-65]. Urinary diversion or vesicostomy are resorted to before transplantation to stabilize and improve kidney function. Availability of different effective and save treatment modalities made it unacceptable that a child with NBD to develop renal impairment, the variety of option facilitate safe and effective control of the deleterious effect of NBD on the upper tract.

Conclusion

Neurogenic bladder dysfunction in children must be diagnosed early in life and the child should receive the proper management, neglecting the case or improper management would end with deleterious effect on the upper tract that end with renal dysfunction and chronic kidney failure. There are different options for management. The type of management would be personalized for every case and could be changed accordingly.

Conclusion

Neurogenic bladder dysfunction in children would end with deleterious effect on the upper tract that end with renal dysfunction and chronic kidney failure that would indicate dialysis or kidney transplantation. Choice of proper management will differ from one child to another, where the management would be personalized. Clean intermittent catheterization(CIC) combined with oral oxybutynin is the basic and standard treatment. Children who receive oxybutynin and developed develop adverse effects that led to discontinuation of treatment would shift intravesical oxybutynin. The new anti-muscarinic drugs who reported to have minimal adverse effect, high tolerability, availability of solution form, and dose adjustment. Mirabegron is a β_3 -adrenoceptor agonist which is a promising drug for children with NBD. Children who develop adverse events from antimuscarinics, β_3 -adrenergic agonist drugs, or non-compliant to CIC, would be candidate for detrusor muscle injection with onabotulinumtoxinA which proved to be safe with no adverse effects.

Percutaneous tibial nerve stimulation is an emerging modality for treatment of NBD in children, it has no adverse effects, accepted by the child and parents. Kidney transplantation would be the last resort for treatment of NBD in children when the have progressive deterioration of kidney function are the child did not respond to measurement. The type of management for NBD in children would be personalized for every case and could be changed accordingly.

- c) The article has no cohesion in the presentation of the results.

Answer: Results had been added and conclusion was upgraded.

- d) The style of the article should be improved. For example, there are different line spacing. The text is not justified.

Answer: The style improved, redundancy was removed, line spacing were adjusted, and spacing were corrected.

Letter To the Editor,

Thank you for your valuable remarks that improved the text form and content.

4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

Answer: The manuscript was edited by native-English speaker who is a Professor of English in the University, grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability were corrected.

5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly. Now we list the abbreviations rules as follows.

Title: Please spell out any abbreviation in the title. Abbreviations are not permitted.

Answer: Considered.

Running title: Please shorten the running title to no more than 6 words. Abbreviations are permitted.

Answer: Considered.

(3) Abstract: Abbreviations must be defined upon first appearance in the Abstract. Examples: Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*).

Answer: Considered.

(4) Key words: Abbreviations must be defined upon first appearance in the Key words.

Answer: Considered.

(5) Core tip: Abbreviations must be defined upon first appearance in the Core tip. Examples: Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

Answer: Considered.

(6) Main Text: Abbreviations must be defined upon first appearance in the Main Text. Examples:
Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

Answer: Considered.

(7) Article Highlights: Abbreviations must be defined upon first appearance in the Article Highlights.
Examples: Example 1: Hepatocellular carcinoma (HCC).

Example 2: *Helicobacter pylori* (*H. pylori*)

Answer: Considered.

(8) Figures: Please verify the abbreviations used in figures and define them (separated by semicolons) at the end of the figure legend or table; for example, BMI: Body mass index; CT: Computed tomography.

Answer: No figures.

(9) Tables: Please verify the abbreviations used in tables and define them (separated by semicolons) at the end of the figure legend or table; for example, BMI: Body mass index; CT: Computed tomography.

Answer: was done.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

- (1) Science editor:** 1. Scientific quality: The manuscript focusses on the lower urinary tract dysfunction in pediatrics progress to CKD in adolescents and young people. The topic is within the scope of the World Journal of Nephrology (WJN). (1) Classification: Grade C, Grade C. (2) Summary of the Peer-Review Report: (1) The abstract it is not clear; (2) The article is not well structured; (3) The article has no cohesion in the presentation of the results; (4) The style of the article should be improved. (3) Format: There is no figure and table. (4) References: A total of 65 references are cited, including 6 references published in the last 3 years; (5) Self-cited references: There is no self-cited reference. 2. Language evaluation: Classification: Grade A, Grade B. There is no language editing certificate. 3. Academic norms and rules: The Conflict-of-Interest Disclosure Form, the signed Informed Consent Form, the Biostatistics Review Certificate, the Institutional Review Board Approval Form are not provided. No academic misconduct was found by the Google/Bing search. 4. Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJN. 5. Issues raised: (1) The "Author Contributions" section is missing. Please provide the author contributions; (2) The format of references needed to be revised according to journal's demands. 6. Re-Review: Required. 7. Recommendation: Major revision.

Answer: Peer-Review Report 1,2,3 items were considered and were answered accordingly.

3-Format: There is no figure and table

Answer: table was added.

4. There is no language editing certificate.

Answer: The manuscript was re-edited by a native-English speaker, University professor.

3. Academic norms and rules:

The Conflict-of-Interest Disclosure Form.

Answer: submitted.

4. The signed Informed Consent Form, the Biostatistics Review Certificate, the Institutional Review Board Approval Form are not provided.

Answer: Not applicable, the text is a "Review article".

No academic misconduct was found by the Google/Bing search. 4. Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJN. 5. Issues raised:

(1) The "Author Contributions" section is missing. Please provide the author contributions;

Answer: author contribution was added in the text.

(2) The format of references needed to be revised according to journal's demands.

Answer: References were revised according to Journal style.

References

1. Kari JA. Neuropathic bladder as a cause of chronic renal failure in children in developing countries. *Pediatr Nephrol.* 2006;21:517–20. [PubMed: 16511684]
2. Filler G, Gharib M, Casier S, Lödige P, Ehrich JH, Dave S. Prevention of chronic kidney disease in spina bifida. *Int Urol Nephrol.* 2012;44:817–27. [PubMed: 21229390]
3. Amarante MA, Shrensel JA, Tomei KL, Carmel PW, Gandhi CD. Management of urological dysfunction in pediatric patients with spinal dysraphism: Review of the literature. *Neurosurg Focus.* 2012;33:E4. [PubMed: 23025445]
4. Bauer SB. Neurogenic bladder: Etiology and assessment. *Pediatr Nephrol.* 2008;23:541–51. [PMCID: PMC2259256] [PubMed: 18270749]
5. Lavallée LT, Leonard MP, Dubois C, Guerra LA. Urodynamic testing - Is it a useful tool in the management of children with cutaneous stigmata of occult spinal dysraphism? *J Urol.* 2013;189:678–83. [PubMed: 22982430]
6. Drzewiecki BA, Bauer SB. Urodynamic testing in children: Indications, technique, interpretation and significance. *J Urol.* 2011;186:1190–7. [PubMed: 21849190]
7. Bauer SB, Hallett M, Khoshbin S, Lebowitz RL, Winston KR, Gibson S, et al. Predictive value of urodynamic evaluation in newborns with myelodysplasia. *JAMA.* 1984;252:650–2. [PubMed: 6737668]
8. Baskin LS, Kogan BA, Benard F (1990) Treatment of infants with neurogenic bladder dysfunction using anticholinergic drugs and intermittent catheterisation. *Br J Urol* 66:532–534
9. Fernandes E, Reinberg Y, Vernier R, Gonzales R (1994) Neurogenic bladder dysfunction in children: review of pathophysiology and current management. *J Pediatr* 124:1–7
10. Jeruto A, Poenaru D, Bransford R (2004) Clean intermittent catheterisation: overview of results in 194 patients with spina bifida. *Afr J Pediatr Surg* 1:20–23
11. Kari JA (2006) Neuropathic bladder as a cause of chronic renal failure in children in developing countries. *Pediatr Nephrol* 21:517–520

12. Coupland CAC, Hill T, Denning T, Morriss R, Moore M, Hippisley- Cox J. Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control Study. *JAMA Intern Med.* 2019;24. [Epub ahead of print].

13. Schröder A, Albrecht U, Schnitker J, Reitz A, Stein R. Efficacy, safety, and tolerability of intravesically administered 0.1% oxybutynin hydrochloride solution in adult patients with neurogenic bladder: A randomized, prospective, controlled multi-center trial. *Neurourol Urodyn.* 2016;35(5):582-588.

References

1 **Kari JA.** Neuropathic bladder as a cause of chronic renal failure in children in developing countries. *Pediatr Nephrol.* 2006;21:517–20. [PMID: [1651168](#)]

2 **Filler G,** Gharib M, Casier S, Lödige P, Ehrich JH, Dave S. Prevention of chronic kidney disease in spina bifida. *Int Urol Nephrol.* 2012;44:817–27. [PMID: [21229390](#) DOI: [10.1007/s11255-010-9894-5](#)]

3 **Amarante MA,** Shrensel JA, Tomei KL, Carmel PW, Gandhi CD. Management of urological dysfunction in pediatric patients with spinal dysraphism: review of the literature. *Neurosurg Focus.* 2012 ;33:E4. [PMID: [23025445](#) DOI: [10.3171/2012.7.FOCUS12232](#)]

4 **Bauer SB,** Neurogenic bladder: etiology and assessment. *Pediatr Nephrol.* 2008 ;23:541-51. [PMID: [18270749](#) DOI: [10.1007/s00467-008-0764-7](#)]

5 **Lavallée LT,** Leonard MP, Dubois C, Guerra LA. Urodynamic testing--is it a useful tool in the management of children with cutaneous stigmata of occult spinal dysraphism? *J Urol.* 2013 ;189:678-83. [PMID: [22982430](#) DOI: [10.1016/j.juro.2012.08.203](#)]

6 **Drzewiecki BA,** Bauer SB. Urodynamic testing in children: indications, technique, interpretation and significance. *J Urol.* 2011 ;186:1190-7. [PMID: [21849190](#) DOI: [10.1016/j.juro.2011.02.2692](#)]

7 **Bauer SB,** Hallett M, Khoshbin S, Lebowitz RL, Winston KR, Gibson S, Colodny AH, Retik AB. Predictive value of urodynamic evaluation in newborns with myelodysplasia. *JAMA.* 1984 3;252:650-2. [PMID: [6737668](#)]

8 **Baskin LS,** Kogan BA, Benard F. Treatment of infants with neurogenic bladder dysfunction using anticholinergic drugs and intermittent catheterisation. *Br J Urol.* 1990;66:532-4. [PMID: [2249125](#) DOI: [10.1111/j.1464-410x.1990.tb15004.x](#)]

9 **Fernandes ET,** Reinberg Y, Vernier R, Gonzalez R. Neurogenic bladder dysfunction in children: review of pathophysiology and current management. *J Pediatr.* 1994 ;124:1-7. [PMID: [8283355](#) DOI: [10.1016/s0022-3476\(94\)70245-4](#)]

10 **Stein R,** Bogaert G, Dogan HS, Hoen L, Kocvara R, Nijman RJM, Quadackers JSLT, Rawashdeh YF, Silay MS, Tekgul S, Radmayr C. EAU/ESPU guidelines on the management of neurogenic bladder in children and adolescent part I diagnostics and conservative treatment. *Neurourol Urodyn.* 2020 ;39:45-57. [PMID: [31724222](#) DOI: [10.1002/nau.24211](#)]

11 **Kari JA.** Neuropathic bladder as a cause of chronic renal failure in children in developing countries. *Pediatr Nephrol.* 2006;21:517-20. [PMID: [16511684](#) DOI: [10.1007/s00467-006-0034-5](#)]

12 **Coupland CAC,** Hill T, Denning T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control Study. *JAMA Intern Med.* 2019; 179:1084-1093. [PMID: [31233095](#) DOI: [10.1001/jamainternmed.2019.0677](#)]

13 **Schröder A,** Albrecht U, Schnitker J, Reitz A, Stein R. Efficacy, safety, and tolerability of intravesically administered 0.1% oxybutynin hydrochloride solution in adult patients with neurogenic bladder: A randomized, prospective, controlled multi-center trial. *Neurourol Urodyn.* 2016 ;35:582-8. [PMID: [25754454](#) DOI: [10.1002/nau.22755](#)]

6. Re-Review: Required.

Answer: done

7. Recommendation: Major revision

Answer: Revision was done accordingly.

- (2) ***Company editor-in-chief:*** I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Nephrology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, the author(s) must add a table/figure to the manuscript.

To the Company editor-in-chief

Dear Sir,

Thank you very much for your comments that will improve the manuscript, we added a table which is a good addition to the manuscript, it summarise all the therapeutic modalities of neurogenic bladder dysfunction in children, and shed light on the mode of action and limitation of each modality.

Thank you.