Surveillance, early diagnosis and intervention for children with cerebral palsy in low resource settings: Lessons from Bangladesh and Vietnam

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THESIS STATEMENT OF ORIGINALITY

This is to certify that to the best of my knowledge the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Signature

Date: 30 Jun 2021

ABSTRACT

Cerebral palsy (CP), the most common physical disability of childhood, is estimated to be more prevalent in low and middle-income countries (LMICs). The pathways and risk factors for CP in LMICs are believed to differ in low resource settings. This in addition to a range of key factors including delayed diagnosis; lack of evidence-based early intervention programs; poor or no access to rehabilitation and assistive devices; often result in greater severity of CP and associated impairments compared to high income countries.

This doctoral research aims to: (i) better understand the clinical characteristics of children with CP in Bangladesh with a specific focus on hip dysplasia and epilepsy, (ii) explore pathways to improve age at diagnosis of CP in Bangladesh, (iii) enhance interventions for children with CP and their primary caregivers through a quasi-experimental study assessing the outcome of an existing program in Bangladesh and (iv) describe CP in another low resource setting, Vietnam, using an alternative epidemiological tool, hospital-based surveillance.

This thesis describes two robust methodologies of data collection on children with CP in LMICs and affirms substantial burden of CP and associated impairments i.e., hip dysplasia, epilepsy, and malnutrition among children with CP in Bangladesh and Vietnam. It maps the path towards the establishment and use of national CP registers in low resource settings. Strategies for early detection and a promising early intervention program for children with CP and their families in Bangladesh, a typical LMIC, have also been described. The findings from this doctoral research have significant bearing in informing practice policy and research in low resource settings globally.

AUTHORSHIP ATTRIBUTION

This thesis includes six papers in total: four published papers, one under review and one ready for submission.

Chapter 1 of this thesis includes the published paper,

Karim T, Al Imam MH, Golland P, Khan AI, Hossain I, Smithers-Sheedy H, Badawi N, Muhit M, Khandaker G. Hip dysplasia among children with spastic cerebral palsy in rural Bangladesh. BMC Musculoskeletal Disorders. 2019 Dec 1;20(1):494.

Author role: I was the lead and corresponding author on this paper. I conducted the data analysis and data interpretation of the study. I wrote the draft and incorporated edits to the manuscript. I responded to comments from reviewers during the publication process with input from supervisors.

Chapter 2 of this thesis includes the includes the publication under review,

Karim T, Das MC, Muhit M, Badawi N, Khandaker G, Mohammad SM. Improving epilepsy control among children with Cerebral Palsy in rural Bangladesh. [Submitted to BMJ Open].

Author role: I was the lead and corresponding author on this study. I supported and contributed to the study design, development of the study materials and overall conduct of the study. I completed data analysis, and interpretation of the data. I wrote the draft and incorporated edits to the manuscript. I responded to comments from reviewers during the publication process with input from supervisors.

Chapter 3 of this thesis includes the published paper,

Karim T, Scherzer A, Muhit M, Badawi N, Khandaker G. Use of a Developmental Milestone Chart (DMC) in Rural Bangladesh to Educate Health Workers and Stimulate Referral for Early Diagnosis and Intervention. Journal of Tropical Pediatrics. 2019 Oct;65(5):505-9.

Author role: I was the lead author on this paper. I coordinated the study activities and conducted data analysis and interpreted the data. I wrote the first draft and incorporated edits to the manuscript. I responded to comments from reviewers during the publication process with input from supervisors.

Chapter 4 of this thesis includes the publication nearly ready for submission,

Karim T, Muhit M, Jahan I, Galea C, Smithers-Sheedy H, Badawi N, Khandaker G. Outcome of community-based parents led early intervention for children with cerebral palsy in rural Bangladesh - a quasi-experimental study.

This will be submitted for publication on a special issue of Brain Sciences journal titled, Early Detection and Early Intervention Strategies for Cerebral Palsy in Low and High Resource Settings.

Author role: I was the lead and corresponding author on this paper. I co-designed and co-supervised this study with co-authors. I curated, analyzed, and interpreted the data. I wrote the draft and incorporated edits to the manuscript. I responded to comments from reviewers during the publication process with input from supervisors.

Chapter 5 of this thesis includes the two published papers,

Karim T, Dosseter R, Giang NT, Dung TQ, Son TV, Hoa NX, Van Anh NT, Chau CM, Van Bang, N, Badawi N, Khandaker G, Elliott E. Data on cerebral palsy in Vietnam will inform clinical practice and policy in Low and Middle-Income Countries. Disability and Rehabilitation. Nov 2020.

Author role: I was the lead and corresponding author on this paper. I cleaned, pooled, analyzed and interpreted the data. I wrote the draft and incorporated edits to the manuscript. I responded to comments from reviewers during the publication process with input from supervisors.

Karim T, Jahan I, Dossetor R, Giang NT, Van Anh NT, Dung TQ, Chau CM, Van Bang N, Badawi N, Khandaker G, Elliott E. Nutritional Status of Children with Cerebral Palsy—Findings from Prospective Hospital-Based Surveillance in Vietnam Indicate a Need for Action. Nutrients. 2019 Sep;11(9):2132.

Author role: I was the lead and corresponding author on this paper. I cleaned, pooled, analyzed and interpreted the data. I wrote the draft and incorporated edits to the manuscript. I responded to comments from reviewers during the publication process with input from supervisors.

Appendix A includes the publication,

Khandaker G, Muhit M, Karim T, Smithers-Sheedy H, Novak I, Jones C, Badawi N. Epidemiology of cerebral palsy in Bangladesh: a population-based surveillance study. Developmental Medicine & Child Neurology. 2018 Nov 5.

Author role: I supported ethics applications and reporting on this paper. I was responsible for recruitment and data collection in Bangladesh. I assisted in data entry and analysis. I drafted the initial and revised manuscript along with GK with input from all the co-authors.

For all publications, supervisors and co-authors were involved in assisting with data interpretation and critically revising the manuscripts for important intellectual content.

In addition to the statements above, in the case where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Student name: Dr Tasneem Karim

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Date: 30 Jun 2021

As supervisors for the candidature upon which this thesis is based, we can confirm that the authorship attribution statements above are correct.

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Auxiliary Supervisor Name: Professor Nadia Badawi

Signature

Date: 30 Jun 2021

DEDICATION

Dedicated to *Maa,* my guiding light.

Forever engraved in fond memories, a true inspiration, and a quiet rebel.

আমি চির-বিদ্রোহী বীর —
বিশ্ব ছাড়ায়ে উঠিয়াছি একা চির-উন্নত শির!

ACKNOWLEDGEMENT

Finally, my highest gratitude for the children and their families for generously sharing their stories with us to support work that will benefit future generations in low resource settings across the world. I am pleased to share some of their smiles in my thesis through photos I had the joy of capturing during my doctoral journey.[1]

All human beings are born free and equal in dignity and rights.
Article 1, United Nations Universal Declaration of Human Rights

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[1] Informed written consent has been obtained for all the photos included in this thesis

TABLE OF CONTENTS

PREFACE

PUBLICATIONS INCLUDED IN THIS THESIS

1. Khandaker G, Muhit M, Karim T, Smithers-Sheedy H, Novak I, Jones C, Badawi N. Epidemiology of cerebral palsy in Bangladesh: a population-based surveillance study. Developmental Medicine and Child Neurology. 2018 Nov 5. [Appendix A]

2. Karim T, Scherzer A, Muhit M, Badawi N, Khandaker G. Use of a Developmental Milestone Chart (DMC) in Rural Bangladesh to Educate Health Workers and Stimulate Referral for Early Diagnosis and Intervention. Journal of Tropical Pediatrics. 2018 Dec 19.

3. Karim T, Jahan I, Dossetor R, Giang NT, Van Anh NT, Dung TQ, Chau CM, Van Bang N, Badawi N, Khandaker G, Elliott E. Nutritional Status of Children with Cerebral Palsy—Findings from Prospective Hospital-Based Surveillance in Vietnam Indicate a Need for Action. Nutrients. 2019 Sep;11(9):2132.

4. Karim T, Al Imam MH, Golland P, Khan AI, Hossain I, Smithers-Sheedy H, Badawi N, Muhit M, Khandaker G. Hip dysplasia among children with spastic cerebral palsy in rural Bangladesh. BMC Musculoskelet Disord. 2019 Oct 27;20(1):494.

5. Karim T, Dosseter R, Giang NT, Dung TQ, Son TV, Hoa NX, Van Anh NT, Chau CM, Van Bang, N, Badawi N, Khandaker G, Elliott E. Data on cerebral palsy in Vietnam will inform clinical practice and policy in Low and Middle-Income Countries. Disability and Rehabilitation. Nov 2020.

6. Karim T, Das MC, Muhit M, Badawi N, Khandaker G, Mohammad SM. Improving epilepsy control among children with Cerebral Palsy in rural Bangladesh. [under review]

7. Karim T, Muhit M, Jahan I, Galea C, Smithers-Sheedy H, Badawi N, Khandaker G. Outcome of community-based parents led early intervention for children with cerebral palsy in rural Bangladesh - a quasi-experimental study. [under review]

FIRST AUTHOR ORAL PRESENTATIONS RELATED TO THIS THESIS

1. Challenges in Setting up a Data Registry in Low and Middle-income Countries: Bangladesh Experience. 1st Congress of Pediatric Alliance and Cerebral Palsy Alliance, 14 - 16 Sep, Hunan, China

2. Karim T, Dossetor R, Giang NH, Anh NV, Dung TQ, Chau CM, Badawi N, Bang NV. Khandaker G, Elliott E. Novel data on cerebral palsy in Vietnam will inform clinical practice and policy. Sydney Vietnam Symposium, 21 Sep, The University of Sydney Business School, Sydney, Australia

3. Karim T, Dossetor R, Giang NH, Anh NV, Dung TQ, Chau CM, Badawi N, Bang NV. Khandaker G, Elliott E. Novel data on cerebral palsy in Vietnam will inform clinical practice and policy. Sydney Vietnam Research Innovation Showcase: 13 Dec 2018, Hanoi, Vietnam

4. Karim T, Das MC, Muhit M, Badawi N, Khandaker G, Mohammad SM. Improving epilepsy control among children with Cerebral Palsy in rural Bangladesh. 31st Annual meeting of the European Academy of Childhood Disability (EACD), 23 – 25 May 2019, Paris, France

5. What Works for Early Intervention Implementation in Diverse Low Resource Settings? Experiences from Bangladesh, India And Uganda. International Society on Early Intervention Conference (ISEI), 25 - 28 Jun 2019, Sydney, Australia [Workshop]

6. Karim T, Jahan I, Imam MHA, Das MC, Muhit M, Badawi N, Khandaker G. Cerebral palsy and health inequity in Bangladesh: Findings from the Bangladesh Cerebral Palsy Register. 74th Annual Meeting of the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM), 23-26 September 2020, Virtual Meeting

7. Karim T, Jahan I, Imam MHA, Das MC, Muhit M, Badawi N, Khandaker G. Cerebral palsy and health inequity in Bangladesh: Findings from the Bangladesh Cerebral Palsy Register. 32nd Annual meeting of the European Academy of Childhood Disability (EACD), May – June 2021, Virtual Meeting

FIRST AUTHOR POSTER PRESENTATIONS RELATED TO THIS THESIS

1. Dossetor R, Karim T, Giang NH, Anh NV, Dung TQ, Chau CM, Badawi N, Bang NV. Khandaker G, Elliott E. Novel data on cerebral palsy in Vietnam will inform clinical practice and policy. 72nd Annual Meeting of the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM), 9-13 October 2018, Cincinnati, Ohio, USA

2. Karim T, Muhit M, Jahan I, Galea C, Smithers-Sheedy H, Badawi N, Khandaker G. Outcome of community-based parents led early intervention for children with cerebral palsy in rural Bangladesh - a quasi-experimental study. 72nd Annual Meeting of the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM), 9-13 October 2018, Cincinnati, Ohio, USA

3. Karim T, Jahan I, Dossetor, Giang N, Anh NV, Dung T, Chau C, Thuong NV, Badawi N, Bang NV, Khandaker G, Elliott E. Nutritional status of children with cerebral palsy: findings from hospital-based surveillance in Vietnam. 73rd Annual Meeting of AACPDM, 18-21 September 2019, Anaheim, California, USA

4. Karim T, Das MC, Muhit M, Badawi N, Khandaker G, Mohammad S. Improving epilepsy control among children with Cerebral Palsy in rural Bangladesh. 73rd Annual Meeting of the AACPDM, 18-21 September 2019, Anaheim, California, USA

AWARDS AND FUNDING RELATED TO THIS THESIS

1. First place at the 2016 Life Shots photo contest at the AACPDM 70th Annual Meeting in Hollywood, Florida.

2. American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) 2017, International Travel Scholarship to attend and present at the 71st Annual Meeting of AACPDM, Montreal, Canada.

3. Cerebral Palsy Alliance Research Foundation Career Development Grant 2017 for project titled 'Cerebral palsy (CP) in Bangladesh: towards developing a national CP register, surveillance, early diagnosis and interventions for children with CP in low resource setting'.

4. Travel scholarship from the Sydney Vietnam Academic Leadership Group, University of Sydney to present at the Sydney Vietnam Research Showcase in Dec 2018, Hanoi, Vietnam.

5. Bursary to attend and present at the 31st Annual meeting of the European Academy of Childhood Disability (EACD) held on 23 – 25 May 2019 in Paris, France.

6. Cerebral Palsy Alliance Research Foundation PhD Research Grant 2019 for project titled 'Cerebral palsy (CP) in Bangladesh: towards developing a national CP register,

surveillance, early diagnosis and interventions for children with CP in low resource setting'.

7. Scholarship to present at the Australasian Academy of Cerebral Palsy and Developmental Medicine 10th Biennial Conference 2020 held on 11 - 14 March 2020 in Perth, Australia.

8. Recipient of scholarship from the University of Sydney Postgraduate Research Support Scheme 2020 awarded in July 2020.

9. Cerebral Palsy Alliance Research Foundation PhD Research Grant 2020 for project titled 'Cerebral palsy (CP) in Bangladesh: towards developing a national CP register, surveillance, early diagnosis and interventions for children with CP in low resource setting'.

10. Cerebral Palsy Alliance Research Foundation Project Research Grant 2021 for project titled Evidence based approach to surveillance, early diagnosis, and intervention of children with cerebral palsy in Vietnam (PRG08419, AU$200,230.00 over 3 years) – Principal Investigator.

RELEVANT TRAINING COMPLETED DURING CANDIDATURE

1. Prechtl's Method of the Qualitative Assessment of General Movements Advanced Course, 1 - 4 November 2018, Sydney, Australia.

2. Hammersmith Infant Neurological Examination (HINE) training, 4 November 2018, Sydney, Australia.

RELEVANT PART TIME EMPLOYMENT DURING CANDIDATURE

- Research Assistant [Jul 2018 – July 2019] The University of Sydney Westmead Clinical School, Faculty of Medicine and Health Sydney, Australia.
- Research Officer [Jul 2019 – Sep 2020] Cerebral Palsy Alliance Research Institute, The University of Sydney, Sydney, Australia.

CO-AUTHORED PUBLICATIONS DURING CANDIDATURE

1. Chan J, Wu Y, Wood J, Muhit M, Mahmood M, Karim T, Moushumi F, Jones C, Snelling T, Khandaker G. Burden of Congenital Rubella Syndrome (CRS) in Bangladesh: Systematic review of existing literature and transmission modelling of sero–prevalence studies. Infectious Disorders - Drug Targets. Oct 2018.

2. Khan A, Ashher F, Karim T, Nawar A, Jahan I, Muhit M, Dey A, Beard F, Khandaker G, immunization of mothers of children with cerebral palsy in rural Bangladesh. Infectious Disorders - Drug Targets. Oct 2018.

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4. Power R, Muhit M, Heanoy E, Karim T, Badawi N, Akhter R, Khandaker G. Health-related quality of life and mental health of adolescents with cerebral palsy in rural Bangladesh. PloS one. 2019 Jun 11;14(6):e0217675.

5. Power R, Galea C, Muhit M, Heanoy E, Karim T, Badawi N, Khandaker G. Determinants of health-related quality of life among adolescents with cerebral palsy in Bangladesh. Research Square; 2019 Sep. DOI: 10.21203/rs.2.13888/v1.

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9. Jahan I, Muhit M, Hardianto D, Karim T, Al Imam MH, Das MC, Smithers-Sheedy H, Badawi N, Khandaker G. Nutritional status of children with cerebral palsy in remote Sumba Island of Indonesia: a community-based key informants study. Disability and Rehabilitation. 2019 Oct 25:1-0.

10. Jahan I, Karim T, Al Imam MH, Das MC, Ali KM, Muhit M, Khandaker G. Childhood Disability and Nutrition: Findings from a Population-Based Case Control Study in Rural Bangladesh. Nutrients. 2019 Nov;11(11):2728.

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12. Power R, Galea C, Muhit M, Heanoy E, Karim T, Badawi N, Khandaker G. What predicts the proxy-reported health-related quality of life of adolescents with cerebral palsy in Bangladesh? BMC public health. 2020 Dec 1;20(1):18.

13. Jahan I, Al Imam MH, Karim T, Muhit M, Hardianto D, Das MC, Smithers-Sheedy H, Badawi N, Khandaker G. Epidemiology of cerebral palsy in Sumba Island, Indonesia. Developmental Medicine and Child Neurology. 2020 Jul 20.

14. Power R, Wiley K, Muhit M, Heanoy E, Karim T, Badawi N, Khandaker G. 'Flower of the body': menstrual experiences and needs of young adolescent women with cerebral palsy in Bangladesh, and their mothers providing menstrual support. BMC Women's Health. 2020 Dec;20(1):1-9.

CO-AUTHORED PRESENTATIONS DURING CANDIDATURE

1. Jahan I, Al Iman MH, Karim T, Muhit M, Hardianto D, Das MC, Smithers-Sheedy H, Badawi N, Khandaker G. Epidemiology of cerebral palsy in remote Sumba Island of Indonesia: Findings from a community-based Key Informant Method (KIM) survey. 31st Annual meeting of the European Academy of Childhood Disability (EACD), 23 – 25 May 2019, Paris, France [Poster].

2. Jahan I, Karim T, Das MC, Muhit M, Smithers-Sheedy H, Badawi N, Khandaker G. Mortality among Children with Cerebral Palsy (CP) in rural Bangladesh: Results from the Bangladesh CP Register (BCPR). 31st Annual meeting of the European Academy of Childhood Disability (EACD), 23 – 25 May 2019, Paris, France [Poster].

3. Dossetor R, Karim T, Giang NH, Anh NV, Dung TQ, Chau CM, Badawi N, Bang NV. Khandaker G, Elliott E. Novel data on cerebral palsy in Vietnam will inform clinical practice and policy. 31st Annual meeting of the European Academy of Childhood Disability (EACD), 23 – 25 May 2019, Paris, France [Poster].
4. Karim T, Muhit M, Jahan I, Galea C, Smithers-Sheedy H, Badawi N, Khandaker G. Outcome of community-based parents led early intervention for children with cerebral palsy in rural Bangladesh - a quasi-experimental study. 31st Annual meeting of the European Academy of Childhood Disability (EACD), 23 – 25 May 2019, Paris, France [Poster].
5. Muhit M, Karim T, Jahan I, Imam MHA, Das MC, Khandaker G. Epidemiology of eye diseases among children with disability in rural Bangladesh: findings from the Shahjadpur Children's Cohort. 73rd Annual Meeting of AACPDM, 18-21 September 2019, Anaheim, California, USA [Poster].
6. Jahan I, Muhit M, Hardianto D, Karim T, Imam MHA, Das MC, Smithers-Sheedy H, Badawi N, Khandaker G. Nutritional status of children with cerebral palsy in remote Sumba Island of Indonesia: a community-based key informants study. 73rd AACPDM 18-21 September 2019, Anaheim, California, USA [Poster].
7. Muhit M, Jahan I, Imam MHA, Karim T, Ghose R, Das MC, Chhetri AB, Khandaker G. Epidemiology of cerebral palsy in Gorkha district of Nepal: findings from a community-based Key Informant Survey. 73rd Annual Meeting of the AACPDM, 18-21 September 2019, Anaheim, California, USA [Poster].
8. Jahan I, Al Iman MH, Karim T, Muhit M, Hardianto D, Das MC, Smithers-Sheedy H, Badawi N, Khandaker G. Community based Key Informants Method (KIM) survey of children with cerebral palsy in rural Sumba Island of Indonesia. 72nd Annual Meeting of the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM), 9-13 October 2018, Cincinnati, Ohio, USA [Oral Presentation].
9. Jahan I, Karim T, Das MC, Muhit M, Smithers-Sheedy H, Badawi N, Khandaker G. Mortality among Children with Cerebral Palsy (CP) in rural Bangladesh: Results from the Bangladesh CP Register (BCPR). 72nd Annual Meeting of the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM), 9-13 October 2018, Cincinnati, Ohio, USA [Oral Presentation].
10. Jahan I, Al Iman MH, Karim T, Muhit M, Hardianto D, Das MC, Smithers-Sheedy H, Badawi N, Khandaker G. Nutritional Status of Children with Cerebral Palsy (CP) in Remote Sumba Island of Indonesia. 31st Annual meeting of the European Academy of Childhood Disability (EACD), 23 – 25 May 2019, Paris, France [Oral Presentation].

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▪ Research Affiliate [Jul 2019 – present] The University of Sydney Westmead Clinical School, Faculty of Medicine and Health Sydney, Australia.

- Student Theme Leader, Disability and Chronic Disease theme of the Sydney Global Child Health Network, a joint initiative by the Discipline of Child and Adolescent Health and the Sydney School of Public Health at the University of Sydney.
- Member, Cerebral Palsy Alliance Research Committee [Jun – Sep 2020].
- Member, Scientific Review Panel of the Australian Paediatric Surveillance Unit.
- Member, Australasian Academy of Cerebral Palsy and Developmental Medicine.
- Member, American Academy for Cerebral Palsy and Developmental Medicine.
- Member, European Academy of Childhood Disability.
- Member, International Society on Early Intervention.
- Member, Ethics Committee of the Asian Institute of Disability and Development.
- Academic Member, Sydney Vietnam Initiative, Sydney Southeast Asia Centre, University of Sydney.

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACPR	Australian cerebral palsy register
BCPR	Bangladesh cerebral palsy register
CP	Cerebral palsy
GLM-CPR	Global low-and middle-income country cerebral palsy register
GMA	General movement assessment
GMFCS	Gross motor functional classification system
HIC	High income country
HINE	Hammersmith infant neurological examination
LMIC	Low and middle-income country
PAEDS	Paediatric Active Enhanced Disease Surveillance
SCPE	Surveillance of Cerebral Palsy in Europe

KEY WORDS

Cerebral palsy

Population-based surveillance

Hospital-based surveillance

Bangladesh

Vietnam

Low resource settings

Low and middle-income country

INTRODUCTION AND RESEARCH FOCUS

OVERVIEW

This thesis constitutes a series of papers with supplementary text to describe the body of work completed as part of the doctoral program. The epidemiology, clinical characteristics, and associated impairments of cerebral palsy (CP) are described, with concurrent exploration of measures for early identification and intervention for children with CP in low resource settings. This chapter includes the background to this doctoral research, the outline of the chapters and the concept map for the thesis.

BACKGROUND

Following the completion of my Bachelor of Medicine and Bachelor of Surgery and Master of Public Health in Bangladesh, I was eager to contribute to the preventive sphere. Contributing to the wellbeing of marginalized populations, a sentiment I fostered from my parents' example in their work in the medical field, has been central to my career aspirations. I was drawn to opportunities that would enable me to work with children, particularly in roles and organizations supporting children with disability and their families. During my search for employment in the new yet familiar world of public health, I was intrigued by an available position at CSF Global (www.csf-global.org).

CSF Global, an independent not-for-profit organisation, is committed to the establishment of a rights-based inclusive society for children with disability in developing countries. The core activities of the organisation constitute multidisciplinary research and generation of high-quality scientific evidence to inform practice, policy, and service delivery. CSF Global was recruiting for the implementation of the Health-Related Quality of Life of Children with Cerebral Palsy in Rural Bangladesh study (Bangladesh CPQoL study). Thus, began my journey in CP research as the Research Program Manager of a highly productive multidisciplinary team at CSF Global in early 2016.

My initial role was to support the Bangladesh CPQoL study, Dr Rosalie Power's doctoral research describing the health-related quality of life, mental health, and sexual and

reproductive health of adolescents with CP in rural Bangladesh, and mental health of their primary caregivers. Alongside this role, I had the opportunity to contribute to a range of ongoing research projects and related service programs at CSF Global. This role enabled me to gain an in depth understanding of the various challenges of one of the most marginalized populations in the world, children with disability and their families in low-and middle-income countries (LMICs) such as Bangladesh with a special focus on CP.

CEREBRAL PALSY

Definition

CP is the most common cause of physical disability in childhood. It is a heterogenous condition, both in causation and clinical characteristics. The definition of CP underwent several changes as the understanding of CP advanced over the years. The most recent and widely used definition of CP defines it as "a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour; by epilepsy, and by secondary musculoskeletal problems".(1) Due to the multidimensional nature of the condition and the advent of knowledge, there is continuing debate on the definition of CP.(2)

Burden of cerebral palsy

According to global estimates there are an astounding 50 million people with CP worldwide.(3) This estimate however, predominantly relies on data from high income countries (HICs) due to the overall dearth of evidence on the epidemiology of CP from LMICs where the burden of CP is disproportionately higher. Available research from LMICs report a range of rates of CP.(4, 5) These differences are in part due to variation in case definition which is unsurprising due to the heterogeneity of the condition. Methodological differences (i.e. population-based versus institution/hospital-based data) also contribute to these differences.(6, 7) Generation of population representative data using standard/harmonised definition of CP is therefore imperative for true estimates of the burden of CP from LMICs.

Classifications of cerebral palsy

The motor impairments of CP are classified into four main subtypes: spastic, dyskinetic, ataxic and hypotonic. Spastic CP, the most common type of CP, is further classified into monoplegia, diplegia, triplegia and quadriplegia based on the distribution of motor impairment.

The severity of motor impairment of CP is widely classified into five subgroups using the Gross Motor Functional Classification System (GMFCS); level I: walks without limitations, level II: walks with limitations, level III: walks using a hand held mobility device, level IV: self-mobility with limitations, may use powered mobility, and level V: transported in a manual wheelchair.(8)

CP is classified into two groups based on the timing of the injury responsible for causing CP: prenatal/perinatal and postnatal. However, understanding the complex causal pathway of CP is challenging.(9)

Risk factors for cerebral palsy

A variety of risk factors of CP spanning from preconception to post neonatal period have been identified. Yet they are often difficult to dissect for the development of appropriate preventive strategies.(10, 11) Recent studies from LMICs show that some risk factors/antecedents of CP (i.e. hypoxic ischaemic encephalopathy, severe neonatal jaundice/kernicterus, low birth weight, intrauterine growth retardation and infections) are more common in low resource settings.(4, 12-14) Public health measures and perinatal care to prevent CP with concurrent temporal data collection on the incidence of CP through long standing CP registers have proven to be instrumental in gaining a better understanding of causal pathways of CP and monitoring trends in HICs.(15, 16) With the emerging CP registers such initiatives are now possible in LMICs.(4) Furthermore, the role of socioeconomic factors on the risk factors of CP will additionally have significant bearing on prevention, causation and clinical outcomes of CP in low resource settings.(17-20)

CEREBRAL PALSY REGISTERS

Long standing CP registers in high income settings, such as Australia and Europe, enable reporting of robust data on the incidence, prevalence, aetiologies, risk factors and temporal

trends over decades.(21, 22) Such data is indispensable to the design and success of preventive strategies, interventions, and they inform policy and service delivery models. Furthermore, CP registers continue to serve as the sampling frame for further research to advance the knowledge of CP across the world [10]. The merits of CP registers are apparent from the declining birth prevalence of CP on HICs. According to the most recent international reports, there has been an astounding 35.0% decline over a 15-year period owing to multifaceted factors including a variety of strategies (i.e. improved perinatal care, antenatal magnesium sulphate, therapeutic hypothermia, the increased uptake of early detection and consequent early intervention) informed by evidence from CP registers.(15, 23) It is now anticipated that with such continued success, there will be further decline in the rates of CP in HICs and result in a shift in focus to the preventive sphere in LMICs.(15)

Better understanding of the risk factors and aetiopathogenesis of CP, in addition to the ensuring implementation of preventive strategies and improved perinatal care, has resulted in reported declines in prevalence in HICs and the changing epidemiology of CP.(15, 23) Working towards the replication of these successes in LMICs is imperative. Lessons from HICs such as Australia where reduced birth prevalence and the lowest rates of CP are observed can accelerate breakthroughs in prevention, treatment and cure for CP globally.(22) It is encouraging that the exponential increase in childhood CP research in the recent decades is extending into the LMICs where majority of the burden is observed.

In the absence of such rigorous studies reporting population-based findings from LMICs, data from HICs and extrapolation of institution-based findings were often used to estimate the burden and the diverse health care needs of children with CP. Prior to the commencement of this doctoral program in 2018, there was an overall lack of scientific evidence on CP in Bangladesh. In particular, there were gaps in the knowledge of CP in the areas of epidemiological research, effective intervention, and service utilization. There is an urgent need to gain a better understanding of the etiology of CP in these settings. Contemporary data on the severity and associated impairments of CP, rehabilitation status is also invaluable for the identification and implementation of appropriate strategies for children living with CP. The majority of the known risk factors of CP continue to prevail in LMICs. In the era of increasingly available evidence and the successes observed in other parts of the world,

addressing the known preventable risk factors for CP in LMICs is warranted. The majority of the known risk factors of CP continue to prevail in LMICs.

Population-based CP registers are a powerful tool for epidemiological research(24) and generate the most accurate data for of incidence, prevalence, risk factors and temporal trends.(25) There are over 40 CP registers across the world, predominantly in HICs. Long standing CP registers have yielded robust data over decades and significantly enhanced our knowledge on the epidemiology of CP and enabled monitoring of trends with advances in medicine, public health initiatives, preventive strategies, interventions, and disability inclusive policies. These registers are powerful tools for advocacy, in the strategy to describe aetiology, prevent CP and find evidence-based treatments.(26) There is a dire need for representative population data to support researchers, clinicians, service providers and policy makers for an evidence-based approach to prevention, early detection, and intervention for CP, particularly in LMICs.

We therefore focused our efforts on developing and utilizing a population-based surveillance of children with CP, the Bangladesh Cerebral Palsy Register (BCPR), to generate vital data. The BCPR study is a collaboration between Cerebral Palsy Alliance Research, the University of Sydney, Australia and CSF Global, Bangladesh and funded by the Cerebral Palsy Alliance Research Foundation. This study and further research inspired by the findings from the BCPR forms the core part of the research and related services for children with CP that I contributed to as part of my roles at CSF Global, the University of Sydney and Cerebral Palsy Alliance Research Institute prior to and during my doctoral candidature. This experience fostered my interest in registers and the tremendous potential they hold in generation of robust data to facilitate evidence-based approaches to interventions and future projects to enhance the wellbeing of children with CP and their families in low resource settings.

RESEARCH CONTEXT: BANGLADESH

Bangladesh, officially the People's Republic of Bangladesh, has been an independent nation since the liberation war in 1971. It is a south east Asian riverine country on the Bay of Bengal, bordered predominantly by India, and a short border with Myanmar (Figure 1).[2]

Although a small country spread across 148,460 square kilometres, it is the 8th most populous country in the world with a population density of ~1161 people per square kilometre, with highest density observed in and around the capital of Dhaka. ~166 million people reside in

Figure 1. Map of Bangladesh

Bangladesh; the median age of the population is 26.3 years. Bengali is the mother tongue of the entire population of Bangladesh apart from the indigenous minority groups.

Bangladesh has eight divisions and 64 districts, these however, have a limited role in public policy. For the purposes of local government, the country is divided into 577 sub-districts (upazillas) including the metropolitan thanas.(27)

Once the second poorest country in the world, Bangladesh has since shown remarkable strides in poverty reduction and reached the lower-middle-income status in 2015.(28) Bangladesh is one of the fastest growing economies in the world in the past decade.(28) Yet a mere 3.0% of the gross domestic product accounted for the total health expenditure per capita.(29) As a result, a significant proportion of health expenditure is out of pocket expense within the pluralistic health system of Bangladesh.(30, 31) This further contributes to the

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[2] Image source : https://www.britannica.com/place/Bangladesh

challenges of meeting the complex health care needs of people with CP and associated impairments.

BANGLADESH CEREBRAL PALSY REGISTER

In 2015, recruitment into the BCPR commenced in a rural sub-district of Bangladesh (i.e. Shahjadpur) and the BCPR study protocol was published for wider dissemination.(32) This was soon followed by the expansion of the CP register to other parts of Bangladesh, and the first population-based data from an LMIC CP register defining the epidemiology was published which I co-authored during my doctoral candidature.(33) The published manuscript is included in *Appendix I*. The BCPR is an ongoing surveillance program generating robust data on prevalence, sociodemographic and clinical characteristics, risk factors, nutrition, education, and rehabilitation status of children with CP in Bangladesh.

BCPR Study Site

The BCPR covers a defined geographical area, the Shahjadpur subdistrict of Sirajganj located in the northern part of Bangladesh. The known denominator population in the study area has enabled population-based estimations using the BCPR data.

The study site, Shahjadpur, has 296 villages with an estimated 70,998 households. It has a total population of 561,076 (child population ~ 226,114) and 12,117 live births per annum.(34)

BCPR Case Definition

CP case definition was based on the Surveillance of CP in Europe and Australian CP Register.(35, 36) This enables the use of any definition for CP including the following five key elements common to the published definitions.

Cerebral palsy:

i. Is an umbrella term for a group of disorders,

ii. Is a condition that is permanent but not unchanging,

iii. Involves a disorder of movement and/or posture and of motor function,

iv. Is due to a non-progressive interference, lesion, or abnormality, and

v. The interference, lesion, or abnormality originates in the immature brain.

BCPR Case Ascertainment

Children with suspected CP were identified using the Key Informant's Method (KIM).(32, 37) This method involves the engagement and training of local volunteers who reside in the same community as the potential study participants i.e., children with CP, thus enabling recruitment from the communities. The Key Informants received structured training on the identification of children with suspected CP. The Key Informants then identified and listed potential cases from their communities and informed the families of the date and venue of the upcoming medical assessment camps within their vicinity.

BCPR Assessment and Data Collection

The medical assessment camps were conducted on a regular basis in the study area. The children identified by the Key Informant underwent clinical assessment for confirmation of the diagnosis of CP by the medical assessment team prior to registration into the BCPR. A multidisciplinary medical assessment team including a paediatrician, a physiotherapist, and a counsellor conducted a detailed medical assessment for data collection. The BCPR registration form, a modified version of the Australian CP Register record form, was used to collect information on perinatal history, clinical characteristics and risk factors for CP. Neurological types of CP, along with Gross Motor Function Classification System (GMFCS)(38) and Manual Ability Classification System (MACS) levels,(39) were assessed and documented.

Anthropometric measurements were taken using standard measuring instruments and guidelines for the assessment of nutritional status. Detailed methodology and relevant study findings on the nutritional status of the BCPR cohort has been reported in a separate study not included in this thesis.(40)

Data on the presence and severity of associated impairments including epilepsy, visual, hearing, speech, and intellectual impairments were documented based on review of limited available medical records, report by the parents or primary caregivers of the children with CP, and clinical assessment by the medical assessment team. Information on sociodemographic characteristics, education and rehabilitation status were collected to identify the diverse needs of the children with CP and their families in Bangladesh.

BCPR Study Findings

The BCPR has enabled comprehensive epidemiological exploration and generated population-based data on children with CP in Bangladesh.(33) Between January 2015 and December 2016, 726 children with CP were identified and registered in the BCPR. The mean age was 7.6 years (standard deviation [SD] 4.5 years) and 38.2% were female. The observed prevalence was 3.4 per 1000 children (95% confidence interval [CI]: 3.2–3.7), resulting in an estimated 233,514 children (95% CI: 219 778–254 118) with CP in Bangladesh. The mean age at the time of diagnosis of CP was 5.2 years (SD 3.8 years), which is substantially delayed compared to HICs and well beyond the age of optimal neuroplasticity of the brain.(41)

The type of CP was predominantly (79.6%) spastic CP of whom 25.6% (n=186) had quadriplegia. In total, 68.2% (n=495) were described as Gross Motor Functional Classification System (GMFCS) level III to V. 79.6% had at least one associated impairment; speech 67.6%, intellectual 39.0%, epilepsy 23.7%, visual 10.2%, and hearing 10.2%. The majority (78.2%) had never received any form of rehabilitation. Causes of CP in Bangladesh comprised potentially modifiable aetiologies. Perinatal causes of CP included intrapartum-related neonatal respiratory depression, neonatal encephalopathy, and infections; while post-neonatal causes included infection, drowning, and trauma.(33)

The BCPR is an ongoing surveillance which continues to generate robust data and facilitate further research and services for children with CP and their families in Bangladesh. This expansive amount of work has led to international collaborations for the initiation of work on CP registers and surveillance in low resource settings across the world.(4) Different study methodologies have been adopted for the collection of different but equally valuable data from several countries. While population-based surveillance such as the BCPR is the best source of epidemiological data,(24, 33) institution-based studies also yield valuable insights. They are an alternative method of data collection as part of locally available services or medical checkups which yield data collected with different aims. One such study, a hospital-based surveillance of children with CP in Vietnam, have been described in Chapter 5 of this thesis.(42-44)

THESIS OUTLINE AND AIMS

The BCPR which was modelled on the Australian CP Register is considered the prototype of CP registers in LMICS and has enabled estimates of prevalence, facilitated clinical surveillance, and continues to inform future research and promote translational research to improve the lives of children with CP and their families in Bangladesh. This thesis addresses some of the gaps identified through the initial BCPR study.(33) Key findings and the ensuing research stimulated by the BCPR study constitute this thesis. These have been summarized in the following thesis outline and thesis concept map.

The *Introduction and Research Focus* described the background to this thesis. It introduces the state of the evidence on CP in Bangladesh with the specific focus on the BCPR study and demonstrates that CP registers are a useful tool for framing disability research even in LMIC settings.

Through the BCPR study, we identified that a substantial burden of CP among children in Bangladesh with a prevalence of 3.4 per 1000 children resulting in an estimates 233,514 children with CP in the country. Furthermore, we identified the following important areas that require further exploration:

- A substantial burden of CP among children in Bangladesh with a prevalence of 3.4 per 1000 children resulting in an estimates 233,514 children with CP in the country
- Greater severity of motor impairments compared to HICs; 25.6% had quadriplegia and 68.2% were described as GMFCS level III to V
- Substantial burden of associated impairments including epilepsy reported among 23.7% of the children
- Delayed diagnosis at 5.2 years of age
- Limited opportunities for interventions for CP with a mere 21.8% of the children receiving any form of rehabilitation

This doctoral research focuses on addressing some of these gaps. The overall aim of this thesis is to describe the clinical characteristics of CP, with concurrent exploration of measures for early identification and intervention for children with CP in low resource settings.

The aims of the thesis are to:

i. Better understand the clinical characteristics of children with CP in Bangladesh with a specific focus on hip dysplasia (*Chapter 1*) and epilepsy (*Chapter 2*)

ii. Explore pathways to improve age at diagnosis of CP in Bangladesh (*Chapter 3*)

iii. Enhance interventions for children with CP and their primary caregivers in Bangladesh through a quasi-experimental study assessing the outcome of an existing program in Bangladesh (*Chapter 4*)

iv. Describe CP in another low resource setting using an alternative epidemiological tool through a hospital-based surveillance in Vietnam (*Chapter 5*)

Gaps	Aims	Thesis Chapter and Manuscript	Key Findings
Limited population representative data on CP from LMICs such as Bangladesh	To examine the prevalence, clinical features, and risk factors for CP in Bangladesh	**Introduction and Research Focus**	• Prevalence: 3.4/1000 children, 233,514 children with CP in Bangladesh • Majority had preventable risk factors • Greater severity of impairments • Diagnosis is delayed • Limited opportunities for early intervention
Burden and severity of CP in low resource settings	To describe the burden of hip dysplasia from a population-based study in Bangladesh	**Chapter 1.** *Hip dysplasia among children with spastic cerebral palsy in rural Bangladesh*	• 40 children with spastic CP (80 hips) had pelvic X-Rays • 62.5% GMFCS level III-V • 20% had hip subluxation
Burden of associated impairments including epilepsy	To define the prevalence and seizure subtypes among children with CP in rural Bangladesh and explore barriers to optimum epilepsy control	**Chapter 2.** *Improving epilepsy control among children with Cerebral Palsy in rural Bangladesh*	• 62.0% had ongoing epileptic seizures; none with prolonged seizures had an emergency seizure management plan. • Non-epileptic events were being pharmacologically treated as seizures in 18.1% • Financial constraints were the main reason for non-compliance
Diagnosis of CP in low resource settings	To explore the feasibility of the use of the DMC to assess childhood neurodevelopment as part of regular medical check ups	**Chapter 3.** *Use of developmental milestone chart (DMC) in rural Bangladesh to educate health workers and stimulate referral for early diagnosis and intervention*	• Diagnosis of CP is delayed in low resource settings • DMC can be used for developmental screening as part of regular health check-ups in low resource settings
Ways for early intervention and rehabilitation of children with CP in low resource settings	To evaluate the outcome of an existing program for children with CP and their primary caregivers in a rural subdistrict of Bangladesh.	**Chapter 4.** *Outcome of community-based parents led early intervention for children with cerebral palsy in rural Bangladesh: A quasi-experimental study*	• A community-based early intervention and rehabilitation program in low-resource setting is effective in improving motor outcomes and speech of children with CP as well as helping with the depressing, anxiety and stress of their primary caregivers
Lack of data on epidemiology and clinical features of CP from other LMICs	To identify children with CP and describe their clinical characteristics in Vietnam To assess the burden of malnutrition and the underlying risk factors among children with CP in Vietnam	**Chapter 5.** *Data on Cerebral Palsy in Vietnam: Findings from Prospective Hospital-Based Surveillance in Vietnam* *Nutritional Status of Children with Cerebral Palsy: Findings from Prospective Hospital-Based Surveillance in Vietnam*	• Children predominantly had spastic CP (95.2%) • Most (69.6%) were quadriplegic • 60.3% were GMFCS level III-V • 28.9% underweight and 29.0% stunted • Significantly greater odds of underweight among children aged >5 years •Underweight and/or stunting high among children with quadriplegia (81%, 84.5%) and GMFCS level IV–V

THESIS CONCEPT MAP

| | AIMS | KEY FINDINGS |

1 High burden & severity of CP in Bangladesh

To describe the burden of hip dysplasia in Bangladesh

- 20% had hip dysplasia

2 High burden of epilepsy among children with CP

To define the prevalence & seizure subtypes among children with CP in rural Bangladesh & explore barriers to optimum epilepsy control

- 62% had ongoing seizures; none with prolonged seizures had an emergency plan
- 18.1% had non-epileptic events treated as seizures
- Financial constraints caused non-compliance

3 Delayed diagnosis of CP at 5.3 years of age in Bangladesh

To explore the feasibility of DMC for neurodevelopmental screening as part of regular health check-ups

- DMC can be used for developmental screening as part of regular health check-ups

→ *To evaluate the feasibility of best practice tools for early diagnosis of CP in Bangladesh as part of a funded ongoing study*

4 Limited opportunities for early intervention in Bangladesh

To evaluate the outcome of an existing program for children with CP & their primary caregivers in Bangladesh

- this intervention is effective in improving,
- motor outcomes and speech of children with CP
- mental wellbeing of their primary caregivers

5 Lack of such vital data from other LMICs

- To identify children with CP & describe their epidemiology in hospital-based settings
- To assess the burden of malnutrition & its risk factors among children with CP

- 95.2% had spastic CP: 69.6% quadriplegic & 60.3% GMFCS levels III-V
- 28.9% underweight & 29.0% stunted

→ *To maintain the existing hospital-based surveillance & promote best practices for CP in Vietnam; funded study for three years commencing July 2021*

BANGLADESH CP Register

CHAPTER 1. HIP DYSPLASIA AMONG CHILDREN WITH SPASTIC CEREBRAL PALSY IN RURAL BANGLADESH

1.1 INTRODUCTION

Children with CP are at risk of developing progressive hip displacement.(45) It is the second most common musculoskeletal deformity among children with CP, more commonly observed among children with more severe functional limitations.(45) Several studies have confirmed a strong relationship between the risk of hip displacement and functional ability of children with CP as classified by the GMFCS and those with spastic quadriplegia.

Findings from the BCPR study showed that majority of the children with CP in Bangladesh had severe functional impairments (23.7% GMFCS IV and 22.9% GMFCS V) and the majority (79.6%) have spastic CP of whom a substantial proportion (25.6%) of the children were reported to have spastic quadriplegia.(33) Thus, a significant proportion of these children were at high risk of hip displacement. However, population-based data on hip dysplasia in children with CP from Bangladesh were not available.

In this study we aimed to describe the burden of hip dysplasia among children with CP in Bangladesh using a population-based CP register (i.e. BCPR) as the sampling frame.

1.2 PAPER #1 *HIP DYSPLASIA AMONG CHILDREN WITH SPASTIC CEREBRAL PALSY IN RURAL BANGLADESH*

RESEARCH ARTICLE   **Open Access**

Hip dysplasia among children with spastic cerebral palsy in rural Bangladesh

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Abstract

Background: Hip dysplasia is common among children with cerebral palsy (CP), particularly in spastic CP. It can result in pain, reduced function and quality of life. However, the burden of hip dysplasia among children with CP in llow-and middle-income countries (LMICs) like Bangladesh is unknown. We aimed to define the burden of hip dysplasia among children with spastic CP in Bangladesh.

Methods: This study includes a subset of the Bangladesh CP Register (BCPR) study cohort who were registered between January and March 2015. The BCPR is a population-based surveillance of children with CP (aged < 18 years) operating in a northern sub-district (Shahjadpur; child population ~ 226,114) of Bangladesh. Community-based key informant's method (KIM) survey conducted to identify children with CP in the surveillance area. A diagnosis of CP was made based on clinical history and examination by the study physicians and physiotherapist. Study participants had an antero-posterior (AP) X-ray of their pelvis. The degree of subluxation was assessed by calculating the migration percentage (MP).

Results: During the study period, 196 children with CP were registered, 144 had spastic CP. 40 children with spastic CP (80 hips) had pelvic X-Rays (mean age 9.4 years, range 4.0–18.0 years) and 32.5% were female. Gross Motor Function Classification System (GMFCS) showed 37.5% ($n = 15$) with GMFCS level I-II and 62.5% ($n = 25$) with GMFCS level III-V. Twenty percent ($n = 8$) of the children had hip subluxation (MP: 33–80%). Osteopenic changes were found in 42.5% ($n = 17$) children.

Conclusions: To the best of our knowledge this is one of the first studies exploring hip dysplasia among children with spastic CP in Bangladesh. Our findings reflect that hip dysplasia is common among children with spastic CP. Introduction of hip surveillance programmes is imperative for prevention of secondary complications, reduced function and poor quality of life among these children.

Keywords: Hip dysplasia, Cerebral palsy, Children, Bangladesh, Surveillance

Background

Cerebral palsy (CP) is a heterogenous group of conditions that affects the developing brain, resulting in a permanent non-progressive dysfunction of the central nervous system manifested by disorders of motor function, movement, and posture [1]. It is the leading cause of childhood physical disability globally affecting two to three children per thousand live births [2, 3]. However, the burden of CP is even higher in low-and middle-

income countries (LMICs). Recent population-based studies from Bangladesh and Uganda reported population prevalence of CP as 3.4 and 2.9 per 1000 children respectively [4, 5].

The motor disorders of CP are often associated with musculoskeletal anomalies [6], of which hip displacement is the second most common abnormality preceded only by the abnormalities of the foot and ankle. It affects nearly one-third of the children with CP and the incidence varies from 1.0% in children with spastic hemiplegia, up to 75.0% in those with spastic quadriplegia [7, 8]. Progressive hip displacement leading to dislocation can be catastrophic and result in extreme

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Karim *et al. BMC Musculoskeletal Disorders* (2019) 20:494

Page 2 of 7

pain, reduced function and quality of life [9, 10]. Other complications include severe contracture, pelvic obliquity and scoliosis, resulting in poor sitting, standing and walking abilities [9, 11, 12]. Most of the studies on hip dysplasia among children with CP are reported from high-income countries, and mostly from areas with an existing hip surveillance programme. However, there is limited data on hip dysplasia from LMICs such as Bangladesh where the burden of CP is substantially high [4].

Studies recommend that radiological screening of children with spastic quadriplegia [13] and GMFCS level IV and V [14] should commence from less than 18 months of age [13]. It is also recommended that children with CP with a migration percentage (MP) of 33 to 40 should undergo radiological examination at 6 months interval prior to surgery [13]. Early detection and management of hip dysplasia can maintain flexible, properly located and pain-free hips with availability of symmetrical range of movement [15]. Introduction of formal surveillance programmes has demonstrated a significant reduction in the incidence of hip dislocation in populations of children with CP in high-income countries [14]. Hip dysplasia and dislocation are preventable through early identification and intervention [8]. However, the burden of hip dysplasia among children with CP in LMICs such as Bangladesh is unknown.

We aimed to describe the burden of hip dysplasia among a population-based cohort of children with CP in rural Bangladesh using the Bangladesh CP Register (BCPR) to inform clinicians and public health professionals [16].

Methods
Study design, setting and participants
This study is a part of the BCPR project. BCPR is one of the first population-based CP registers in a LMIC setting and has been ongoing since January 2015 in a northern part of Bangladesh i.e. Shahjadpur (child population ~ 226,114) [17]. Children with CP registered with the BCPR were identified using a novel method, the Key Informant Method (KIM) which involves training of local volunteers to serve as key informants (KIs) and list children with CP from their community. The children then undergo detailed clinical assessment by a multidisciplinary team for confirmation of diagnosis and registration into the BCPR. The details of the BCPR study has been described previously [4, 16].

Between January and March 2015, a sub-group of the BCPR registrants were included in this study. Due to limited available resources, every third child from the BCPR cohort with spastic CP was selected for radiological assessment. In the event that any prospective study participant was unwilling the next child was approached for participation in the study.

Clinical assessment
Children with CP were identified from the community using the KIM, [18] and a detailed neurological examination was performed by a trained paediatrician and physiotherapist during the clinical assessment and BCPR registration process. Sociodemographic and clinical data were collected using BCPR record forms. Motor type and motor severity including Gross Motor Functional Classification System (GMFCS) levels were determined following standard guideline [19]. The predominant motor type of CP included spastic, dyskinetic or ataxic movement motor types based on clinical assessment by a paediatrician. Spastic topography was further classified as mono/hemiplegic, diplegic, triplegic, and quadriplegic.

Radiological assessment
Children with spastic CP had an anteroposterior (AP) pelvic X-ray. Hip displacement was measured from an AP radiograph of the hips using existing protocol [20]. The degree of subluxation (dysplasia) was assessed by calculating the MP i.e. the percentage of the bony width of the femoral capital epiphysis which falls lateral to a line drawn vertically from the bony lateral margin of the acetabulum, the Perkins line. This technique has been found useful to determine hip dysplasia among children [21]. Studies of validity have shown that a change greater than 8.3% in MP represents a real change in displacement of the femoral head with 95% confidence [20]. The MP found among the subjects were classified as normal hip (MP: <32%), and subluxated hip (MP: 33 – 80%) [22]. Radiological diagnosis of osteopenia was made by the radiologist after qualitative assessment of the X rays. Qualitative features of osteopenic bone included increased radiolucency, vertical striation, end plate thinning and accentuation of cortical margins of any vertebra including changes in shape.

Ethical consideration
The study was approved in Australia by the Cerebral Palsy Alliance NHMRC Human Research Ethics Committee (Ref no. 2015–03–02), and in Bangladesh by the Asian Institute of Disability and Development (AIDD) Human Research Ethics Committee (southasia-irb-2014-l-01) and Bangladesh Medical Research Council (BMRC) HREC (BMRC/NREC/ 2013–2016/1267). Informed written consent was obtained from the primary caregiver of the children prior to recruitment into the study.

Statistical analysis
The data were processed using SPSS (Statistical Package for Social Science, version 22.0 for windows; SPSS Inc., Chicago, IL, USA). The measures of central tendency (mean) and dispersion (SD) were used. Descriptive analyses were done to present the proportion of dysplastic hips according to the background factors (age, sex,

Karim *et al. BMC Musculoskeletal Disorders*   (2019) 20:494

Page 3 of 7

parental education), and degree of motor impairment of the children with CP.

Results

Out of the 196 BCPR registrants during the study period, 73.4% ($n = 144$) had spastic CP of which 40 children underwent radiological assessment. The mean age was 9.4 ± 4.0 years (range 4.0–18.0 years) and 32.5% ($n = 13$) of the study cohort were female.

The majority of the mothers had completed primary education (42.5%, $n = 17$) whereas more than one third of the fathers had not have any education (37.5%, $n = 15$). The median age of diagnosis of CP was 3 years. The majority (37.5%, $n = 15$) of the children had diplegia. 37.5% ($n = 15$) were described as GMFCS level I-II and 62.5% ($n = 25$) as GMFCS level III-V. Large numbers of children with CP (60%, $n = 24$) had not ever received rehabilitation services. Twenty percent ($n = 8$) of the children had hip subluxation of which five children were between 5 to 9 years of age (Table 1).

Hip subluxation and age CP diagnosis, type of CP, GMFCS and rehabilitation status

The majority (75.0%, $n = 6$) of the children who had subluxation of hips were diagnosed with CP between 24 to 47 months of age. Children with subluxated hips had spastic diplegia (50.0%, $n = 4$), quadriplegia (37.5%, $n = 3$) and hemiplegia/monoplegia (12.5%, $n = 1$). Children with GMFCS levels III -V had the highest proportion of subluxated hips; 37.5% (n = 3). Among the children with hip subluxation 62.5% ($n = 5$) never accessed any rehabilitation services (Table 2).

Qualitative findings

On qualitative assessment of the x-rays by a radiologist we found that 42.5% ($n = 17$) of the children had signs of osteopenic changes of which 94.1% ($n = 16$) had mild osteopenia and 5.8% ($n = 1$) had moderate osteopenic changes.

Discussion

The aim of the study was to investigate the burden of hip dysplasia among children with spastic CP from a population-based CP register in rural Bangladesh. We found that a fifth of our cohort had subluxation of hips which has yielded valuable insights into the high burden of hip dysplasia among children with spastic CP in Bangladesh.

Subluxation of hips was more commonly observed among children over 5 years of age and with more severe functional motor limitations (i.e. GMFCS levels III - V). This is consistent with other studies from high income countries which showed that the more severe outcomes of hip dysplasia are observed among older children and

Table 1 Socio-demographic characteristics, age of CP diagnosis, neurological subtype of Spastic CP, gross motor function classifications and rehabilitation status of children with CP

Characteristics	n (%)
Gender	
Male	27 (67.5)
Female	13 (32.5)
Age (years)	
< 5	6 (15.0)
5–9	18 (45.0)
10–14	12 (30.0)
15–18	4 (10.0)
Maternal education	
Illiterate	11 (27.5)
Primary	17 (42.5)
Secondary	9 (22.5)
More than Secondary	3 (7.5)
Paternal education	
Illiterate	15 (37.5)
Primary	10 (25.0)
Secondary	10 (25.0)
More than Secondary	5 (12.5)
Age of diagnosis of CP (months)	
0–23	1 (2.5)
24–47	21 (52.5)
48–84	11 (27.5)
85 & above	7 (17.5)
Spastic subtype	
Hemi/monoplegia	11 (27.5)
Diplegia	15 (37.5)
Triplegia	4 (10.0)
Quadriplegia	10 (25.0)
GMFCS levels	
Level I	5 (12.5)
Level II	10 (25.0)
Level III	12 (30.0)
Level IV	4 (10.0)
Level V	9 (22.5)
Received rehabilitation services	
Yes	16 (40.0)
No	24 (60.0)

among those with higher GMFCS levels [7, 14, 23]. Furthermore, all the children with subluxation of hips in our cohort were diagnosed with CP after 24 months of age and nearly two thirds of them had not ever received any rehabilitation services.

Table 2 Distribution of hip displacement according to socio-demographic factors, spastic CP sub-type, GMFCS and rehabilitation status

	Right		Left		Total	
Age	Normal	Subluxated	Normal	Subluxated	Normal	Subluxated
0–4 years (*n* = 6)	5 (14.3)	1 (20.0)	5 (13.5)	1 (33.3)	10 (13.9)	2 (25.0)
5–9 years (*n* = 18)	14 (40.0)	4 (80.0)	17 (45.9)	1 (33.3)	31 (43.1)	5 (62.5)
10–14 years (*n* = 12)	12 (34.3)	0 (0.0)	11 (29.7)	1 (33.3)	23 (31.9)	1 (12.5)
15 and above (n = 4)	4 (11.4)	0 (0.0)	4 (10.8)	0 (0.0)	8 (11.1)	0 (0.0)
Maternal Education						
Illiterate (*n* = 11)	11 (31.4)	0 (0.0)	11 (29.7)	0 (0.0)	22 (30.6)	0 (0.0)
Primary (*n* = 16)	15 (42.9)	2 (40.0)	15 (40.5)	2 (66.7)	30 (41.7)	4 (50.0)
Secondary (*n* = 9)	7 (20.0)	2 (40.0)	8 (21.6)	1 (33.3)	15 (20.8)	3 (37.5)
More than Secondary (*n* = 3)	2 (5.7)	1 (20.0)	3 (8.1)	0 (0.0)	5 (6.9)	1 (12.5)
Paternal Education						
Illiterate (*n* = 15)	14 (40.0)	1 (20.0)	15 (40.5)	0 (0.0)	29 (40.3)	1 (12.5)
Primary (*n* = 10)	9 (25.7)	1 (20.0)	9 (24.3)	1 (33.3)	18 (25.0)	2 (25.0)
Secondary (*n* = 10)	7 (20.0)	3 (33.3)	9 (24.3)	1 (33.3)	16 (16.7)	4 (50.0)
More than Secondary (*n* = 5)	5 (14.3)	0 (0.0)	4 (10.8)	1 (33.3)	9 (12.5)	1 (12.5)
Age of diagnosis of CP (months)						
0–23 (*n* = 1)	1 (2.9)	0 (0.0)	1 (2.7)	0 (0.0)	2 (2.8)	0 (0.0)
24–47 (*n* = 21)	17 (48.6)	4 (80.0)	19 (51.4)	2 (66.7)	36 (50.0)	6 (75.0)
48–84 (*n* = 10)	10 (28.6)	1 (20.0)	10 (27.0)	1 (33.3)	20 (27.8)	2 (25.0)
85 & above (*n* = 7)	7 (20.0)	0 (0.0)	7 (18.9)	0 (0.0)	14 (19.4)	0 (0.0)
Spastic subtype						
Hemiplegia/ monoplegia (*n* = 11)	11 (31.4)	0 (0.0)	10 (27.0)	1 (33.3)	21 (29.2)	1 (12.5)
Diplegia (*n* = 14)	12 (34.3)	3 (60.0)	14 (37.8)	1 (33.3)	26 (36.1)	4 (50.0)
Triplegia (*n* = 4)	4 (11.4)	0 (0.0)	4 (10.8)	0 (0.0)	8 (11.1)	0 (0.0)
Quadriplegia (*n* = 10)	8 (22.9)	2 (40.0)	9 (24.3)	1 (33.3)	17 (23.6)	3 (37.5)
GMFCS						
I-III (*n* = 27)	25 (71.5)	2 (40.0)	25 (67.5)	2 (66.6)	50 (69.4)	4 (50.0)
IV-V (*n* = 13)	10 (28.6)	3 (60.0)	12 (32.4)	1 (33.3)	22 (30.5)	4 (50.0)
Received rehabilitation services						
Yes (*n* = 24)	23 (65.7)	1 (20.0)	22 (59.5)	2 (66.7)	45 (62.5)	3 (37.5)
No (*n* = 16)	12 (34.3)	4 (80.0)	15 (40.5)	1 (33.3)	2 (37.5)	5 (62.5)

Findings from our study have a bearing on the importance of hip surveillance among children with CP in LMIC settings. Hip dysplasia can be detected early by monitoring through regular hip X-rays to facilitate timely treatment and can thereby avert complications which are detrimental to the quality of life of children with CP and their families [9, 10]. In contrast to high income countries, where a range of treatment options are available for the management of of children with CP, including botulinum toxin injection, bracing, soft tissue release surgery for spasticity, reconstructive surgeries and salvage procedure [24], the prognosis of children with CP is remarkably different in poorer countries where there is

limited access to such services. In addition to the lack of services these children and their families face additional challenges due to socioeconomic factors and rampant stigma around disabilities such as CP [25].

The position of femoral head within the acetabulum up to the age of 5 years is important to ensure stability of the hip and acetabular development [26, 27]. Therefore, early detection of progressively displaced hips and referral for orthopedic management is imperative to prevent further displacement and to keep the femoral head in position within the age of 5 years [28]. However, early diagnosis of hip dysplasia is challenging particularly through physical examination alone. Regular clinical

Karim *et al. BMC Musculoskeletal Disorders* (2019) 20:494

Page 5 of 7

inspection for the range of abduction of the hip, and repeated radiological examination of the hips is necessary to identify hip dysplasia in time [8, 29, 30]. The aim of hip surveillance programmes that are based on the Consensus Statement on Hip Surveillance for Children with Cerebral Palsy is to ensure that progressive hip displacement is detected early enough to enable timely referral for orthopedic assessment and management [31]. Decrease in incidence of hip dislocation has been previously documented with the introduction of hip surveillance programme [13]. Incorporation of hip surveillance into routine care has been recommended for all children with CP. This includes radiological assessment between 12 to 24 months of age with subsequent management varying with gross motor severity i.e. GMFCS levels [14]. Studies also suggested that non-ambulatory children and those who have an annual increment of the MP by more than 7% require more vigilant monitoring and consideration for orthopedic referral [1, 32].

A study conducted in Norway and Southern Sweden compared the burden of hip dislocation among children with CP in regions with and without hip surveillance programmes [20]. The sample size at the two sites ($n = 119$ in Norway and $n = 136$ in Southern Sweden) were comparable to our study cohort of 196 children with CP. The proportion of children at GMFCS levels III-V among both the study populations were substantially lower than our cohort; 34.0% in Norway and 38.0% in Southern Sweden population compared to 62.5% in our study cohort in Bangladesh [20]. It was observed that in Southern Sweden where hip surveillance services are provided the prevalence of hip dislocation was lower, fewer children required surgical intervention and the children underwent hip operations at an earlier age [20]. 20.0% of the children from our cohort had hip subluxation which is comparable to the findings from Norway (15.1%). Whereas Southern Sweden had a significantly lower proportion (0.7%, $p < 0.001$) of children with hip subluxation in presence of a surveillance programme [20].

Early identification of hip dysplasia is limited by the absence of hip surveillance programmes, thereby resulting in a high burden [31, 32]. A recent study conducted in India among 118 children with CP aged 2 to 12 years with GMFCS levels III-V showed that 12.7% had developmental dysplasia of spastic hip [21]. An even higher burden of hip dysplasia (54.7%) was reported in another study conducted in Malaysia [33].

Findings from these studies collectively illustrate the apparent benefits of hip surveillance programmes in the reduction of the burden of hip dysplasia and the aversion of associated complications which drastically impair the wellbeing of children with CP [20, 21, 33]. There is a dire need for prospective hip surveillance programmes for children with CP in LMICs. Our study has direct clinical implication; the established programmes in high income countries and the method described in this study can be incorporated for the management of children with CP in LMICs. As radiological services are becoming increasingly available in semi-rural areas of LMICs such as Bangladesh, it is now possible to develop and implement hip surveillance programmes with a simplified protocol for these settings. Ongoing surveillance of children with CP such as the BCPR can serve as the basis for the implementation of recommended guidelines for hip dysplasia among children with CP in low resource settings. This will ensure early detection of hip dysplasia and subluxation which can thereby facilitate early intervention to avert and limit the adverse outcomes of hip dysplasia.

Study limitations

Despite our best efforts there are several limitations in this study which are inherent to observational studies. The cross-sectional design limited the establishment of causal relations between the independent variables and hip dysplasia. Radiography of hips were undertaken in a position as neutral as possible which was often difficult to achieve owing to spasm or contractures. We had to restrict or study only among children with spastic CP due to budget constraints. However, studies have shown that children with spastic CP are the most affected by hip dysplasia. Advanced statistical analyses were also limited due to the small number of children in subgroups (i.e. eight children with subluxation). Furthermore, caution is recommended in the interpretation of comparisons between studies due to methodological differences.

Conclusion

To the best of our knowledge this is one of the first studies exploring hip dysplasia among children with spastic CP in Bangladesh. Our findings from this selected sample suggest hip subluxation is common among children with spastic CP in rural Bangladesh. Further studies are needed to address the true extent of this complex complication of CP to improve the quality of life and ensure better prognosis among children with CP and their families. Introduction of hip surveillance programmes is imperative for the prevention of secondary complications, reduced function and poor quality of life among these children.

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1.3 CHAPTER SYNOPSIS

In this chapter, the burden of hip dysplasia among children with CP in Bangladesh has been described. The findings show that 20.0% of the children had hip subluxation and 42.5% had osteopenic changes. These finding affirm the importance of a hip surveillance program to reduce functional limitations and avert secondary complications through early detection and intervention for hip dysplasia among children with CP.

Chapter 2 will describe another common associated impairment, epilepsy, among children with CP in Bangladesh.

CHAPTER 2. IMPROVING EPILEPSY CONTROL AMONG CHILDREN WITH CEREBRAL PALSY IN RURAL BANGLADESH
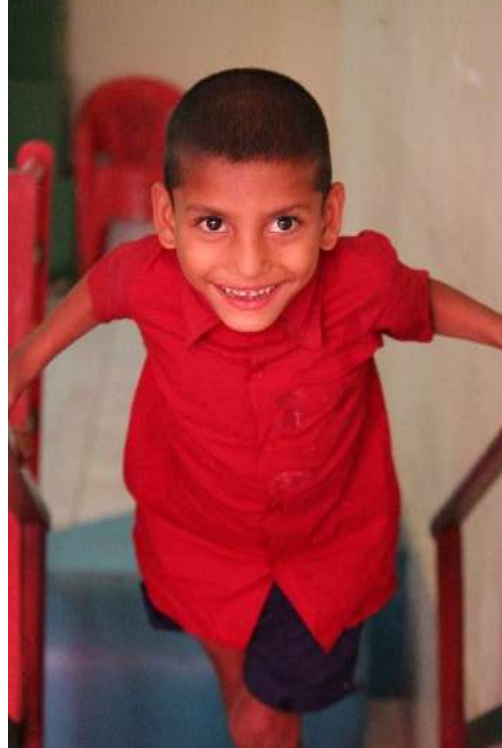
2.1 INTRODUCTION

The original BCPR study findings showed that 23.4% of children with CP had epilepsy.(33) Given the frequency of the epilepsy in this population, in this chapter we sought to further explore this common comorbidity. We identified the prevalence and seizure subtypes in children with CP in Bangladesh. Furthermore, we identified the barriers to optimal epilepsy control in this group of children. This study was a joint collaborative effort between CSF Global, the University of Sydney and Cerebral Palsy Alliance.

2.2 PAPER #2. *IMPROVING EPILEPSY CONTROL AMONG CHILDREN WITH CEREBRAL PALSY IN RURAL BANGLADESH*

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Improving epilepsy control among children with cerebral palsy in rural Bangladesh: A prospective cohort-based study

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Improving epilepsy control among children with cerebral palsy in rural Bangladesh: A prospective cohort-based study

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ABSTRACT

Objective: To define the prevalence and seizure subtypes among children with cerebral palsy (CP) in rural Bangladesh and explore barriers to optimum epilepsy control.

Design: Prospective cohort study

Setting: The study was conducted in Shahjadpur, a rural subdistrict of Bangladesh.

Participants: Children (<18 years) with CP and epilepsy identified using the Bangladesh CP Register in the study site.

Methods: Assessments were conducted in three focused epilepsy clinics overseen by a pediatric neurologist between December 2016 - January 2018, with intervening phone and video-conference follow-ups. Details of event type, frequency and medication compliance were collected. Antiepileptic drugs (AED) were prescribed based on seizure type, family income, comorbidity and medication availability.

Results: 23.4% (170/726) of the BCPR cohort had a clinical diagnosis of epilepsy of whom 166 were assessed. Following the focused epilepsy clinics, 62.0% (103/166) children were clinically determined to have ongoing epileptic seizures. 62.1% (64/103) had generalized tonic clonic seizures, 27.2% (28/103) had focal seizures with altered awareness and 10.7% (11/103) had other seizure types. None of the children with prolonged seizures (31/103) had an emergency seizure management plan. Non-epileptic events were being pharmacologically treated as seizures in 18.1% (30/166) children. Financial constraints were the main reason for non-compliance on follow up.

Conclusions: Gaps in optimum epilepsy management in rural Bangladesh are amenable to improvement anchored with local health care workers. Training and clinical care focused on recognition of common seizure types, seizure mimics and rationalizing use of available AEDs can be facilitated by better referral pathways and telehealth support.

Key Words: Epilepsy, cerebral palsy, Bangladesh, CP

Strengths and limitations of this study

- Children with CP and epilepsy identified through an ongoing population-based surveillance.

- Specialist clinical assessments were conducted overseen by a pediatric neurologist.

- Phone and video-conference follow-ups were conducted.

- The study provided opportunity for continuing local capacity building.

- The clinical diagnoses relied on clinical impression and were not corroborated by investigations.

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INTRODUCTION

Cerebral palsy (CP) is a term that defines a heterogenous group of early-onset, non-progressive, neurodevelopmental disorders secondary to injury to the developing brain [1]. Studies show that epilepsy is associated with greater impairment of cognitive function, poorer motor outcomes, more profound behavioral and psychological problems, and poorer quality of life among children with CP, all of which collectively contribute to a greater burden of disability and care [2]. Children with CP and epilepsy tend to have early onset of seizures which can often be difficult to control [3].

Recent estimates from a population-based study in Bangladesh showed a high burden of CP with an estimated prevalence of 3.4 per 1000 children [4]. Bangladesh is one of the most densely populated and under resourced countries in the world [5]. The World Health Organization (WHO) classified Bangladesh as one of the countries with severe shortages of health workers. There is inequity in the skill mix and distribution of health workers between urban and rural Bangladesh [6]. One of the four axes of the value-based framework for global health delivery highlights the need for alignment of care delivery to the local context [7].

Resources for the diagnosis and management of neurologic disorders such as epilepsy are often limited in low and middle-income countries (LMICs) such as Bangladesh [8]. Several aspects of epilepsy management that may be considered routine in tertiary or specialist settings are not applicable to community-based settings [9]. There is a substantial epilepsy treatment gap in low resource settings owing to a wide spectrum of factors including shortage of doctors particularly in the rural areas,[6] lack of available investigation and inpatient treatment facilities as well as decreased service utilization due to the stigma around a disability diagnosis.[10]

We aimed to define the prevalence, clinical phenotypes and barriers to optimum epilepsy control among children with CP in a community-based setting in Bangladesh.

METHODS AND ANALYSIS

Cohort compilation

We used the Bangladesh CP Register (BCPR); a prospective population-based surveillance of children with CP in Shahjadpur a northern subdistrict of Rajshahi division in Bangladesh for identification of children with CP and epilepsy. Detailed account of the BCPR study protocol and findings have been described in previous publications [4]. During previous BCPR camps, a diagnosis of epilepsy had been

based on history of one or more unprovoked seizures in the previous 3 months recorded by medical practitioners and review of any available medical records [4].

Clinical assessment of epilepsy

Children with CP and epilepsy identified via the BCPR were clinically reviewed in three focused epilepsy clinics held for three days each time at three different locations within the BCPR study site. Specialist clinical assessments at the clinics were overseen by a pediatric neurologist from Australia who travelled to Bangladesh for the focused epilepsy clinics during the study period. Diagnoses of epilepsy and seizure like events were reviewed during assessment in the clinics. Details of seizure/event type, frequency, medication use and compliance were collected according to a predesigned standard proforma (Appendix A). Workflow during the clinic is outlined in Figure 1.

Local capacity building

Two physicians were trained by the pediatric neurologist in classifying seizure types according to the 2017 International League Against Epilepsy (ILAE) guidelines [11], demonstration of clinical signs during the epilepsy clinics, and discussions around seizure mimics and drug choice (Appendix B). One community worker based in the study area was also trained to conduct phone follow ups of the children on antiepileptic drugs (AED).

Selection of antiepileptic drugs

Before the clinics, the community worker collected information on availability and cost of AED in local pharmacies within the study area between December 2016 and January 2018. A dose equivalence table was drawn up for easy prescription in the clinic along with notes on important side effects and interactions. During the clinics, AED were prescribed based on seizure type, medication availability and family income. The approach undertaken for shared decision making in AED prescription is outlined in Figure 2.

Telehealth supported follow up and clinics

Phone follow up

Targeted phone follow ups of the children on AED were conducted by the trained community health worker every three months during the study period, following the initial specialist assessment at the focused epilepsy clinics. The phone follow ups were semi-structured. The design, conduct and the outcome measures for the follow ups were additionally informed by the study team's experience

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and input from the primary caregivers (Appendix C). Seizure control was documented during phone follow ups. In our study seizure control was defined as no reported seizure since the last follow up.

Telemedicine clinics

Telemedicine clinics were initiated in May 2018 and held on a monthly basis using Skype as part of ongoing capacity building to improve epilepsy control among the study cohort. The local trained physician saw the patients face to face in the study site and used a handheld, internet connected tablet to videoconference with the pediatric neurologist in Australia. Patient interview for new and follow up patients followed a set format (Appendix C). New patient data from the telemedicine clinics are not included in this paper.

Patient and Public Involvement

This work was informed by the priorities, experience and preferences of the primary caregivers of the children with CP and epilepsy who participated in the study. The design and implementation of the follow ups, including outcome measures important to the study participants, relied on feedback from families of children with CP and epilepsy. Baseline information was communicated to the primary caregivers by the study team. This informed shared decision making related to the treatment and follow up for their children. Furthermore, the follow ups and telemedicine clinics were conducted by a local community worker and local physician, which enhanced community involvement during and beyond the study.

Statistical analysis

Descriptive analyses were carried out. All statistical analysis was conducted using SPSS version 24 (IBM Armonk, NY, USA).

Ethics

This study was conducted as part of the Bangladesh Cerebral Palsy Register Study which has been approved by the Bangladesh Medical Research Council (BMRC) Human Research Ethics Committee (Ref no. BMRC/NREC/2013–2016/1267) in Bangladesh, and by the Cerebral Palsy Alliance NHRMC Human Research Ethics Committee (Ref no.2015–03-02) in Australia. Written informed consent was taken from the primary caregiver/parents/guardian of the children with CP.

RESULTS

Prevalence and basic demographic characteristics

726 children with CP were registered into the BCPR between January 2015 and December 2016, 23.4% (170/726) of whom had a clinical diagnosis of epilepsy. 166 of these children attended the three focused epilepsy clinics between December 2016 and January 2018 and form the study cohort. 55 (33.1%) were female. The mean age of the children was 6 years 10 months (SD: 4 years 5 months) years.

After the focused epilepsy clinics, 62.0% (103/166) children were clinically determined to have ongoing epileptic seizures based on review of their history, existing medical records and specialist clinical evaluation (Figure 3). Therefore, the revised prevalence of epilepsy among the BCPR cohort during the study period was 14.3%.

Seizure subtypes

62.1% (64/103) had generalized tonic clonic seizures (GTCS), 27.2% (28/103) had focal seizures with altered awareness and 5.8% (6/103) had other seizure types (focal seizures with preserved awareness, epileptic spasms, myoclonic seizures and tonic seizures). Data on seizure type was unclear on history for 4.9% (5/103). At the time of first assessment, seizures were already controlled with AED in 5.8% (6/103) children. 30.1% (31/103) of children had a history of prolonged seizures (>30 minutes) and none of these patients had an emergency seizure plan. Their caregivers tended to wait at home till the seizures settled and did not seek emergency medical assistance due to geographical or financial constraints.

Barriers to optimum epilepsy control

Non-epileptic events among children with CP

Non-epileptic events were determined to have been mislabeled as seizures in 18.1% (30/166) children which included extremity clonus (n=7), dystonic postures (n=6), spasticity related spasms (n=4), breath holding spells (n=3), mannerisms (n=3), sleep related myoclonic jerks (n=2), startles (n=2), stereotypies (n=2) and rhythmic movement disorders in sleep (n=1). 23.3% (7/30) of these children were being treated with AED.

Epilepsy control

Of the 103 children with seizures, 62 were already on AEDs at the time of our clinical review. Polypharmacy with more than two concurrent AED was commonly observed and AED changes were made for the majority of them. Advised AED changes consisted of dose alteration in 54.8% (34/62) and medication change in 17.7% (11/62). 27.4% (17/62) were advised to continue treatment already

initiated by various providers. We initiated treatment for 39/41 children not previously on AED who were clinically determined to still be having epileptic seizures; 2/41 only had short seizures once or twice a year and were not put on AED.

Telehealth supported follow up and clinics

Phone follow up

We were able to review 75.8% (78/90) children with epileptic seizures on follow up during the study period. On follow-up (median 6.0 months), 69.2% (54/78) were taking prescribed medications as advised. Among them 75.9% (41/54) showed improvement in seizure control (>50% seizure reduction), including 14 children who became seizure free. 30.8% (24/78) families had discontinued the advised treatment due to affordability (8/24, 33.3%), excessive drowsiness (7/24, 29.2%), development of a rash (4/24, 16.7%), no perceived benefit with medication and lack of understanding behind the use of regular medications (2/24, 8.3%). Three (3/24, 12.5%) children who discontinued medications were reported to be seizure free. None of the families reported any adverse effects that led to reported cardiorespiratory compromise, hospital presentation or death.

Two children from our cohort died during the follow up period, one due to meningitis and the other due to a lower respiratory tract infection. Their cause of death was determined by verbal autopsy conducted as part of a separate study [12].

Telemedicine

Five telemedicine clinics undertaken in 2018 contributed to patient follow up and clinical capacity building. During these clinics 47 patients were seen by a local medical practitioner with internet-based videoconference support from the pediatric neurologist in Australia. Each clinic was of three hours duration during which patient interview was undertaken in the same manner as in the focused epilepsy clinics. Thirty minutes were marked during each clinic for discussion regarding clinical signs, history taking and AED choice. Clinical details for new patients reviewed during telemedicine clinics were not included in this cohort.

DISCUSSION

Epilepsy is a significant comorbidity in some individuals with CP. Previous studies have described a prevalence of 15-90% epilepsy in CP cohorts [13,14]. Overall, epilepsy contributes more significantly to the global burden of disease in resource poor settings as evident from the 2015 Global burden of disease studies. We found an initial prevalence of epilepsy of 23.4% in our cohort. Interestingly,

following reassessment in our clinics, as described, this was revised to 14.3%. Previous studies have also noted such discrepancy between determination of a clinical diagnosis of epilepsy between specialist and community-based settings with a misdiagnosis of epilepsy being made in as many as 25% of cases [15]. This has flow on impacts as we noted in terms of incorrect, often excessive use of medications. Epilepsy poses substantial economic burden on families [16]. When families devote a significant proportion of their finances, attention, time or all of these towards one aspect of their child's management, other aspects of care such as physical therapy, nutrition, pain and musculoskeletal management are likely to be neglected, more so in resource poor settings [17].

As demonstrated by recent innovative projects in neighbouring Nepal, education of community level workers and general medical practitioners can lead to more consistent clinical diagnosis of epilepsy [18]. In our experience, rationalisation or cessation of medications after focused clinical assessments led to changes in family finances diverted towards medication use. We envision that the development of simplified print and multimedia based educational resources for health care workers and medical practitioners hold the potential to improve epilepsy diagnosis in resource scarce settings such as our study site.

Polypharmacy with more than two concurrent AEDs is unlikely to contribute significantly to seizure control [19]. In countries like Bangladesh with a mismatch of clinical care practices between urban and rural areas, the use of less conventional or alternative medications is very likely to be encountered.

AED availability is very limited in rural Bangladesh [20]. Medications need to be purchased by families and hence, cost per month for AEDs is a significant consideration when choosing medications for chronic use to ensure good compliance. The cheapest and most readily available AEDs are phenobarbitone, clobazam and sodium valproate. If a diagnosis of CP is very likely based on clinical evaluation and history, earlier use of sodium valproate or clobazam in this setting is a viable option for transitioning from phenobarbitone which is most commonly prescribed in infancy. As outlined in our methods and Figure 2, AED choice can be rationalized based not only on the seizure type but also existing comorbidity as some AEDs can help improve comorbid psychiatric symptoms or sleep disturbance.

Our experience highlighted a gap in the recognition and management of prolonged seizures in settings like ours compared to conventional management in urban and resource rich settings.

Benzodiazepines are the mainstay of out of hospital, particularly health worker or parent led management of prolonged seizures. However, midazolam or lorazepam are not available at all in rural Bangladesh. Diazepam is only available in glass ampoules through restricted prescriptions in some pharmacy outlets. In our and wider reported experience caregivers are often reluctant to use glass ampoules or follow several steps in medication administration to a child at home [21]. Other readily available benzodiazepines are cheap (clobazam: 0.042 USD per 10 mg tablet and clonazepam: 0.048 USD per 1 mg tablet; prices mid 2018) but there is very little evidence regarding their use in the setting of prolonged seizures [22,23]. Status epilepticus can significantly add to the burden of cumulative brain injury and therefore warrants a solution [24]. This may be in the form of a per-rectal, oral or, alternative routes for delivery of well-established medications for status epilepticus such as phenobarbitone, valproate or midazolam. Alternatively, the use of medications such as clonazepam drops via open label trials requires urgent exploration for such settings.

Our model has demonstrated that immediate positive impact on epilepsy management and reduction in burden of care on families can be achieved through structured assessments by medical and allied personnel who are trained to assess children for epilepsy and use available medications according to a structured framework. This can be achieved for a population base such as in our study area with limited personnel and without additional investigation or formalized health care facilities, though these would be desirable to further improve patient outcomes. We piloted the use of videoconference-based telemedicine clinics after initial face to face clinics. With some prior training in the use of a structured clinical approach, this method can be very time-efficient in reviewing patients led by a non-specialist medical practitioner/community worker and supported by a specialist. In our experience, this not only provided continuity of clinical support with existing personnel but also provided an opportunity for continuing professional development and capacity building. We hope that in the post-COVID era, implementation and incorporation of telemedicine should be easier and more acceptable to providers, policymakers and the community.

We summarize the key barriers identified and proposed or already implemented solutions in Table 1. Development of multimedia or mobile application-based resources that may simply illustrate clinical assessment of children with epilepsy, examples of non-epileptic events and emergency seizure management will provide convenient means for translation of our findings to the wider population in Bangladesh and, with language translation, to similar resource poor settings across the world.

We have engaged with tertiary paediatric neurology centres in Bangladesh to support some families with requisite investigations or more frequent specialist review. However, this will always be limited to financial and logistic constraints of rural families.

Study limitations

We did not systematically collect baseline investigation information for this cohort as a small proportion had any previous tests such as electroencephalography (EEG) or neuroimaging. The clinical diagnosis of seizures and non-epileptic events were not corroborated by investigations as they were unavailable in this resource limited setting. We had to rely on the clinical impression of a limited number of observers. Although we utilized standard criteria to assess seizure reduction, the collection of the follow up data was based on reporting by the primary caregiver which may have been a source of potential bias.

CONCLUSION

Epilepsy is prevalent among children with CP in rural Bangladesh and the various gaps in optimum epilepsy management are lack regular follow-up, recognition of common seizure types and non-epileptic seizure mimics, familiarization with commonly available, affordable AED and availability of guidelines for prolonged seizure management. These gaps are amenable to proposed low cost, educational interventions. Health care workers can improve epilepsy management with regular follow-up, education on common seizure types, seizure mimics, use of commonly available, affordable AED and guidelines for prolonged seizure management.

AUTHORS' CONTRIBUTION

All listed authors meet the appropriate authorship criteria, and nobody who qualifies for authorship has been omitted. GK and SM conceptualized and established this research study. They also contributed to study design, development of the study materials and overall conduct of the study supported by TK. SM, TK and MCD were responsible for assessment of study participants and data collection. SM, GK and MM provided specialist advice in this study. TK, SM and GK completed data analysis, interpretation of the data and drafted the initial and revised manuscript with input from all the co-authors. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST DISCLOSURES

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

No additional data are available.

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Table 1: Barriers to epilepsy control and suggested interventions

Barriers	Suggested interventions
AED availability	Selection of locally available medications for management through a structured guideline
Lack of skilled personnel for epilepsy management and follow up locally	Capacity building and engagement of local medical practitioners and community health workers Development of multimedia or mobile application-based resources Telemedicine
Affordability	Rationalization of drugs
Poor treatment compliance	Rationalization of drugs Training and engagement of health workers for follow up Caregiver education
Prolonged seizure management	Development of guideline and resources for management of prolonged seizure for training of local health workers
Misidentification of non-epileptic episodes as seizures	Development of video resources describing seizures and non-epileptic events
Lack of parental understanding regarding epilepsy treatment	Parent education on epilepsy treatment

Figure 1: Clinical assessment of epilepsy in children with CP in Shahjadpur

Bangladesh Cerebral Palsy Register
Population-based surveillance of children with cerebral palsy in Shahjadpur

↓

Dates for epilepsy clinics decided

↓

Children with CP having epilepsy identified from the BCPR cohort

↓

Families of the children informed of the clinic date and location by phone by community worker

↓

Epilepsy clinics held at 3 sites in Shahjadpur
  ▪ Structured proforma populated and anthropometric measurement taken by community workers
    10 minutes per patient

  ▪ Clinical review by local medical practitioners overseen by pediatric neurologist from Australia and review of relevant medical records
    15 minutes per patient with interpretation

  ▪ Medications explained by community worker
    5 – 10 minutes per patient

Figure 2: Suggested considerations in choice of medications for seizures and comorbidity in children with cerebral palsy

Choice of medications*

Seizure

Comorbidity/non-epileptic events

Generalized

Focal

Valproate
- *>6 months old, unequivocal history of HIE, no history of developmental regression, no organomegaly or stigmata of mitochondrial disorders
- Comorbid mood lability
- Myoclonic seizures

Clobazam
- Any age, if add on treatment required due to partial control or breakthrough seizures despite use of appropriate doses of another AED
- Standalone use for nocturnal seizures only or fever triggered seizures
- Standalone use for tonic spasms if phenobarbitone or valproate not useful on past trials
- Comorbid sleep disturbance
- Myoclonic seizures

Phenobarbitone
- <6 months old
- could not afford any other medications

Carbamazepine
– preferred if family could afford it

Valproate
- *as before
- preferred if family could not afford carbamazepine or previous adverse effect with carbamazepine

Clobazam
– add on treatment required due to partial control or breakthrough seizures despite use of appropriate doses of another AED

Phenobarbitone
- <6 months old
- could not afford any other medications

Sleep disturbance
- Clonidine
- Clobazam

Behavioral problems
aggression, self-mutilation, disinhibition
- Clonidine
- Valproate
- Lamotrigine
- Carbamazepine

Dystonia
- Trihexiphenidyl
- Levodopa
- Baclofen
- Clobazam

Spasticity
- Baclofen
- Clobazam
- Diazepam
- Orthoses
- Physical therapies

Breath holding
- Iron
- Piracetam
- No treatment

*All medications are listed in order of preference for management

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Figure 3: Study diagram
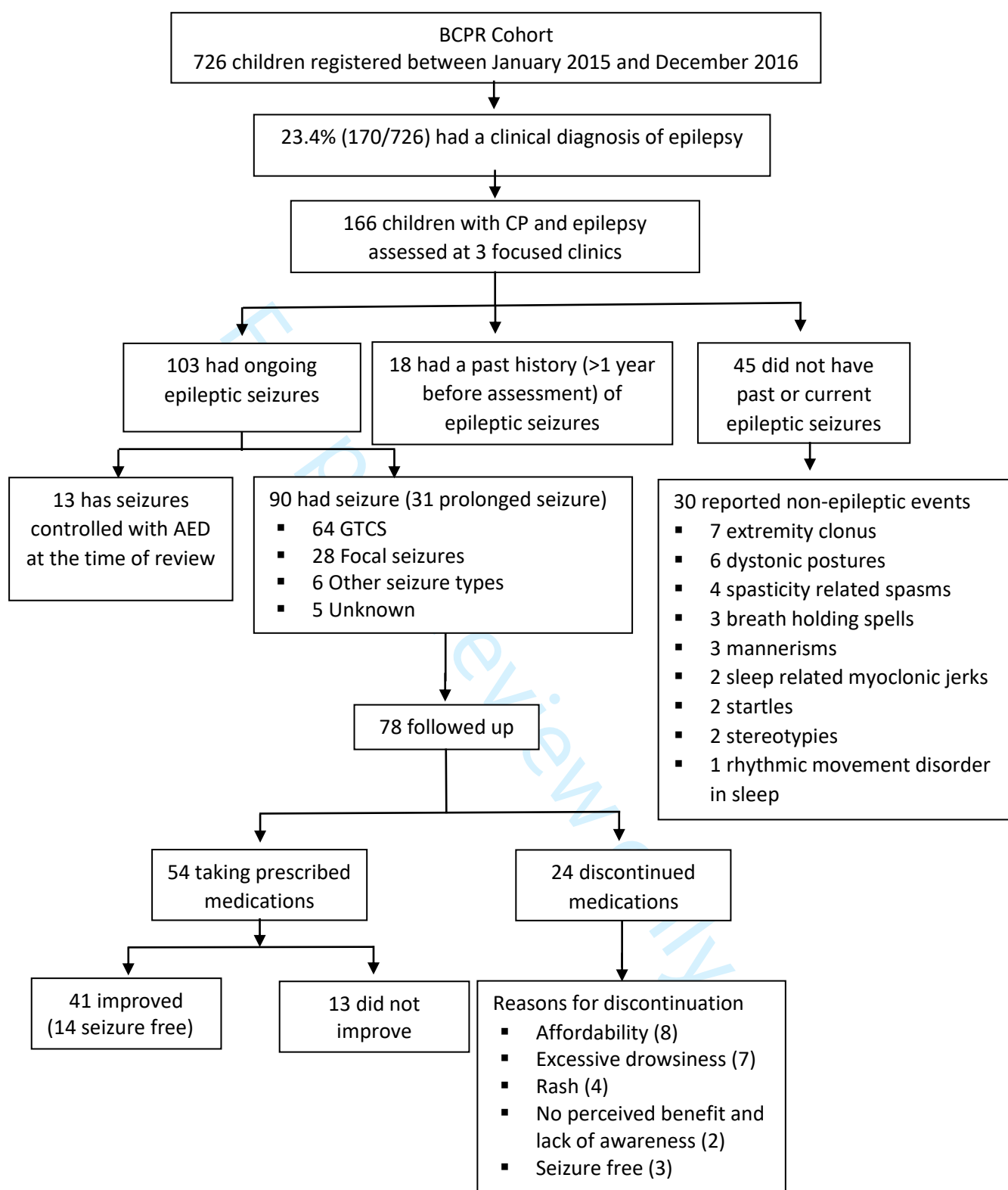
Appendix A: Clinic proforma used during focused epilepsy clinics

ASSESSMENT DETAILS		
ID NUMBER:		**SERIAL NUMBER:**
ASSESSMENT LOCATION:		**ASSESSMENT DATE:** DD / MM / YYYY
CHILD'S DETAILS		
NAME:	**GENDER:** ☐ M ☐ F	**DOB:** DD / MM / YYYY
HEAD CIRCUMFERENCE (cm):	**WEIGHT (kg):**	**LENGTH/HEIGHT (cm):**

FATHER'S DETAILS		
NAME:	**DOB:** DD / MM / YYYY	**OCCUPATION:**
EDUCATION ☐ Illiterate ☐ Primary ☐ Secondary ☐ Higher secondary ☐ Graduation ☐ Post-graduation ☐ Diploma/other trade qualification		

MOTHER'S DETAILS		
NAME:	**DOB:** DD / MM / YYYY	**OCCUPATION:**
EDUCATION ☐ Illiterate ☐ Primary ☐ Secondary ☐ Higher secondary ☐ Graduation ☐ Post-graduation ☐ Diploma/other trade qualification		

CONTACT DETAILS	
DISTRICT:	**SUB-DISTRICT:**
UNION:	**VILLAGE:**
POST CODE:	**PHONE NO.:**

TYPE OF CASE (select one): ☐ New   ☐ Follow-Up

SEIZURE CONTROL: ☐ Same ☐ Better ☐ Worse	**SEIZURE FREE ON TREATMENT:** ☐ Yes ☐ No
COMPLIANT: ☐ Yes ☐ No	**IF NO, REASON FOR NON-COMPLIANCE:**

REASON FOR POOR SEIZURE CONTROL:
MAIN CONCERN:

HISTORY AND EXAMINATION FINDINGS
BIRTH HISTORY:

SEIZURE	
FIRST:	**LAST:**
HISTORY OF PROLONGED SEIZURE (> 5 mins): ☐ Yes ☐ No	
CURRENT FREQUENCY: _____ times per ☐ day ☐ week ☐ month ☐ year	
TYPE:	
DURATION OF SEIZURE:	**DESCRIPTION:**
PREVIOUS MEDICATION & INVESTIGATION	

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Appendix B: Guideline for drug choice at clinics

Table of Contents

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
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MEDICATIONS FOR SEIZURE MANAGEMENT

PHENOBARBITONE

Dose range
- 1–6 mg/kg daily in 1 or 2 doses; start at the lower end of range and increase slowly if required.

Seizure types useful for
- For generalized seizures and focal seizures.
- Recurrent febrile seizures
- Neonatal seizures
- Less likely to help blank staring "absence" seizures

Adverse effects
- Allergic rash, rarely can cause extreme hypersensitivity reaction
- Hyperactivity
- Sedation

Comment
- Generally, a good medication to continue unless it is not working or the side effects are not tolerable
- Do not stop suddenly and wean over several weeks if patient has been on it for more than 3 months

SODIUM VALPROATE

Dose Range
- 20–40 mg/kg daily in 2 divided doses; start at 5-10 mg/kg/day and increase slowly to 20 mg/kg/day. Then increase further if required.

Seizure types useful for
- For all seizure types

Adverse effects
- Hyperactivity
- Liver dysfunction
- Caution with use in children with developmental delay less than two years or older who are likely to not have true CP. Valproate can cause fatal liver dysfunction in those with a history of mitochondrial disorders. This is suggested by a history of developmental regression eg. A child who was able to sit before can no longer do so.

Comment
- Valproate is likely to work for most seizure types and cause less sedation than phenobarbitone
- Valproate works synergistically with clobazam and lamotrigine.
- Lamotrigine should be introduced very cautiously if someone is already on valproate

CLOBAZAM

Dose Range

- Start at 1-2 mg/dose once a day. Can increase as required to
  - 2.5-5 mg BD in children <2 years
  - 5-10 mg BD in children 2-10 years
  - 10 mg TDS in older children
  - maintenance 0.3-1 mg/kg/day in 2 divided doses
- The above doses are a guide and higher doses can be used in younger children if tolerated and if thought to be beneficial for seizure control

Seizure types useful for

- For all seizure types
- Also helpful for dystonia management in some cases

Adverse effects

- Sedation
- Hyperactivity
- Hallucinations
- Drooling

Comment

- Useful monotherapy or add on medication
- Start at small doses like 1 mg BD and grade up
- Can crush tablet and suspend in water to make up small doses if liquid not available
- If difficult for family to understand use quarter tablet / half tablet instead of dissolving
- Wean very slowly similar to phenobarbitone if patient has been taking Clobazam for more than 3 months
- Children can sometimes get used to benzodiazepines. If seizures break through after a few months of good control, then consider swapping over to another benzodiazepine like Nitrazepam.

NITRAZEPAM

Dose Range

- Start at 1 month – 2 years: 0.25mg/kg twice daily, up to 0.5mg/kg twice daily
- The above doses are a guide and higher doses can be used in younger children if tolerated and if thought to be beneficial for seizure control

Seizure types useful for

- For all seizure types
- Infantile spasms

Adverse effects

- Sedation
  - Drooling

Comment
- Useful monotherapy or add on medication
- Start at small doses like and grade up
- Wean very slowly similar to phenobarbitone if patient has been taking Nitrazepam for more than 3 months
- Children can sometimes get used to benzodiazepines. If seizures break through after a few months of good control, then consider swapping over to another benzodiazepine like Clobazam.

CARBAMAZEPINE
Dose Range

- 10–20 mg/kg daily in 2-3 divided doses; start at 2.5-5 mg/kg/day and increase slowly to 10 mg/kg/day. Then increase further if required. Some patients can respond to low doses 5-10 mg/kg/day and can be maintained on these doses without further increasing unless required

Seizure types useful for
- Focal seizures only
- Avoid for generalized, absence and febrile seizures

Adverse effects
- Hyperactivity
- Liver dysfunction

Comment
- Useful drug for focal seizures, e.g. With hemiplegic CP

MEDICATIONS FOR DYSTONIA/SPASTICITY MANAGEMENT

TRIHEXIPHENIDYL/BENZHEXOL
Dose Range
- Start at 0.25 mg once a day and gradually increase to 0.25 mg tds.
- If tolerated, can trial up to 2 mg – 4 mg tds
- In older children, higher doses can be used if benefit is noted

Symptoms useful for
- Mainly for dystonia management. Can also help drooling due to its anticholinergic properties

Adverse effects
- Dry mouth, eyes
- Constipation
- Confusion
- Double vision

- Irritability

Comment
- About 25-50% efficacy for dystonia management if side effects are not a problem. Some children can benefit remarkably more
- Avoid other anticholinergic medications or if any of the adverse effects are already a clinical problem
- If not benefit after maximum doses for 3-4 weeks, then discontinue as delayed benefit is unlikely to occur.

BACLOFEN
Dose Range
- **2-7 y** -10-40 mg/day divided in three to four doses/day. Start: 2.5-5 mg twice a day, may increase by 5-15 mg/day every 3-4 days, Max: 40 mg/day.
- **8-11 y -** Dose: 10-60 mg/day divided in three to four doses/day. Start: 2.5-5 mg twice a day, may increase by 5-15 mg/day every 3-4 days; Max: 60 mg/day.
- **12 y and older -** Dose: 20-80 mg/day PO divided in three to four doses/day. Start: 5 mg twice a day, may increase by 15 mg/day every 2-3 days; Max: 80 mg/day.

Start Symptoms useful for
- Mainly for spasticity management.

Adverse effects
- Hypotonia
- Drooling
- Sedation

Comment
- Baclofen is a good medication for high tone which is due to spasticity
- It is not so good when there is dominant or mixed dystonia
- Relatively high doses may be needed in some patients making side effects intolerable, these have to be balanced with dose
- Other sedative medications will add to sedative effects and drooling – benzodiazepines, phenobarbitone
- Taper and stop slowly over few weeks if patient has been taking Baclofen for more than 3 months.

LEVODOPA/CARBIDOPA
Dose Range
- 1-4 mg/kg/day (levodopa component). Start slowly at 1 mg/kg/day divided in 2 doses and increase to target 4 mg/kg/day in 3 divided doses.
- Can increase further if focal but clear benefit.

Symptoms useful for
- Dystonia management
- Can be very helpful when dystonia shows a trend of worsening as the day progresses or is exercise induced

Adverse effects

- Nausea

Comment

- About 25% efficacy for dystonia management in cerebral palsy but a safe drug to try
- Very useful in genetic dopamine responsive dystonia which can mimic CP but is rare.
- Some preparations are available as Levodopa/Benserazide. Dose guide is same for levodopa component

MEDICATIONS FOR BEHAVIOUR MANAGEMENT

CLONIDINE

Dose Range

- Start at 25 micrograms at night for sleep management
- Can increase to 25-100 microgram three times a day for behavior management

Start Symptoms useful for

- Management of hyperactive or aggressive behavior. e.g. biting, inattentive in school, disturbs other children, fidgety, can't sit still (these symptoms have to be sufficiently severe to be disruptive to daily home or school life to be considered for treatment)
- Also helpful for episodic management of severe dystonia in patients who get periodic worsening. Doses up to 100 micrograms 4-6 times per day can be helpful for short bursts of 3-4 days. Then wean back to baseline doses or stop

Adverse effects

- Sedation
- Sometimes postural dizziness due to postural hypotension – more likely at lower doses

Comment

- Wean slowly over a week if patient has been on clonidine for more than 3 months
- Average efficacy for ADHD, stimulants are better

RISPERIDONE

Dose Range

- 0.25mg – 5 mg/day in children. Try to manage on least efficacious dose

Symptoms useful for

- Management of hyperactive or aggressive behaviour.

Adverse effects

- Increased appetite
- Weight gain
- Metabolic disturbance – hyperlipidemia after years of use
- Extrapyramidal effects like rigidity

Comment
- Try clonidine first
- Can be quite useful if behavioral issues are really disruptive for daily life.

MEDICATIONS FOR EMERGENCY MANAGEMENT

DIAZEPAM

Dose Range
- 0.5 mg/kg <6 y/o; 0.3mg/kg 6-11 y/o; 0.2mg/kg >11y/o

Symptoms useful for
- Management of prolonged seizures >5 min at home.

Adverse effects
- Sedation
- Respiratory depression and arrest
- Local injury

Comment
- Only prescribe if family have received education on use and understand the administration process
- If a child is having a seizure in which he/she is convulsing or is unconscious, it is important to follow simple first aid measures ie. protection from injury, positioning on their side to assist breathing.
- Materials needed
  - a 25ml bottle of diazepam mixed with a stabilizing solution, containing 1mg of diazepam in each 1ml (or alternative concentration)
  - a reusable 10ml syringe
  - a reusable soft plastic tube to attach to the syringe for drawing up and injecting the diazepam
  - a sachet of lubricant jelly

REFERENCES
- Australian Medicines Handbook
- MIMS Australia
- Epocrates
- www.rch.org.au
- www.dhs.winsconsin.gov

Appendix C: Follow up questionnaire

Child's Name:				Gender:	☐ Male ☐ Female
Weight in kg:		Phone No:		DOB:	DD/MM/YYYY
Mother's Name:			Father's Name:		
Assessment Location:				Assessment Date:	DD/MM/YYYY

Check before phone call/follow up clinic:
☐   Medications and doses the child is on   ☐   Was there a change made in the last clinic

Phone Call: ☎
1. Is your child taking the prescribed medication regularly?
   ☐ **No**, is your child taking any other medication? ☐ **Yes** → *Fill up table below* ☐ **No** → *Go to 3*
   ☐ **Yes**, *(Fill up table below)* Has there been any improvements? ☐ **Yes** → G*o to 2* ☐ **No** → G*o to 2*

Name of Medication	Formulation	Dose	Daily Dose Frequency
☐ Valproic acid *[Valex/Epilim/Epilim/Valpro]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Phenobarbitone *[Barbit/Berdinal/Emer/Epinal/Pheno/Phenoba/Phenoson]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Epinephrine *[Adrinor/Adrenaline/Adrin]*	☐ Injection ☐ IV	☐ ___ ml ☐ ___ mg	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Benzodiazepine *[Clonazepam/Clobazam/Alsium/Clob/Clobam/Epson/ Frisium /Epiclon/Epnil/Leptic/Myotril/Rivotril/Rivo]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Clonidine *[Catapres 0.1/Clonipres 0.1]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tab	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Piracetam *[Neurolep/Neuratam/Piratam/Juvain/Piramax]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Baclofen *[Flexifen/Bacofen/Mylofen/Axant/Beclovan]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Trihexyphenidyl *[Hexinor/Trihexy]*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4
☐ Other*(write)*	☐ Syrup ☐ Tablet	☐ ___ ml/___spoon ☐ ___ mg, ___ tabs	☐ 1 ☐ 2 ☐ 3 ☐ 4

2. Is your child seizure free at current dose?
☐ **Yes** → *End*
☐ **No**, Frequency of seizure: _____ per day / week / month / year
            Average duration of seizure _____ minutes/hours

For those **not taking any medicine now**:
3. Has the medicine caused any problem?   ☐ **Yes** → *Fill up table below and end.* ☐ **No** → *Go to 4*.

	Problem	Immediate action on the phone
☐	Extensive rash developed on medication	Stop the medication and need to review urgently
☐	Child too drowsy to feed safely on medication	Reduce to older dose/previous medication
☐	Other Problem:	

4. Specify any other reason for not taking prescribed medication regularly:
   _____

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-6
		(b) Give reasons for non-participation at each stage	Figure 3
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	Figure 3
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA

Discussion

Key results	18	Summarise key results with reference to study objectives	8-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-11

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11-12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

2.3 CHAPTER SYNOPSIS

In this chapter, the prevalence and phenotypes of epilepsy among children with CP in Bangladesh has been described with concurrent exploration of the barriers to optimal epilepsy control.

Following focused epilepsy clinics, 62.0% of the children with CP and epilepsy were clinically determined to have ongoing epileptic seizures. 62.0% had generalized tonic clonic seizures, 27.2% had focal seizures with altered awareness and 10.7% had other seizure types. Non-epileptic events being treated pharmacologically as seizures were found in 18.1% of children. None of these children had an emergency seizure management plan.

The findings highlight the need for such strategies for epilepsy control among children with CP. This work ensured development of local resources and capacity building towards a sustainable model for epilepsy control. This approach to epilepsy control among children with CP in Bangladesh can potentially be scaled up in other low resource settings.

As one of most common associated impairments among children with CP, measures for optimal epilepsy control should be integrated into early intervention and rehabilitation programs for children with CP, particularly in low resource settings. However, early intervention is often limited by delayed diagnosis in LMICs.

Chapter 3 explores strategies for early detection of children with CP in Bangladesh.

CHAPTER 3. EARLY DETECTION OF CHILDREN WITH CEREBRAL PALSY IN BANGLADESH
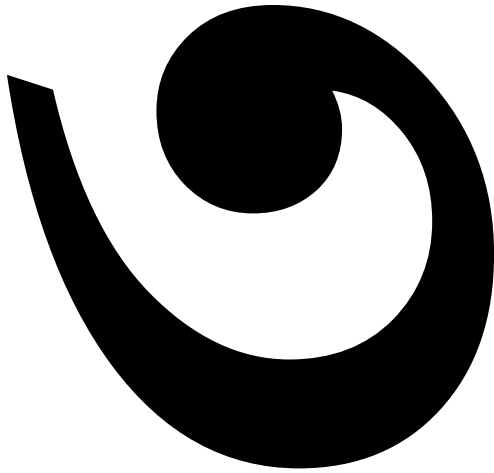
3.1 INTRODUCTION

The diagnosis of CP in Bangladesh is substantially delayed beyond the critical period of optimizing neuroplasticity of the developing brain.(3, 33) Studies from HICs has shown that it is now possible to identify babies at high risk of CP as early as three months of age. This is well before any other signs, such as activity limitations, are evident. However, in the absence of the use of the best practice tools for the early detection of CP i.e., General Movement Assessment, HINE, and neuroimaging, (46) activity limitation associated with delayed developmental milestones, particularly classical motor milestones, are often the first signs of CP or early onset childhood disability in Bangladesh.

The current best practice guideline recommends a shift towards referral for intervention as soon as an infant is identified to be at risk for CP,(47) as an alternative to delaying it until a formal CP description is confirmed later. This will ensure early intervention when the infant brain has the most neuroplastic potential. Although developmental milestones are not predictive of CP, they may serve as a simple screening tool enabling early referral for intervention to timely nurture the developing brain of infants at risk for CP in low resource settings.

In this study the feasibility of a simple tool, the Developmental Milestone Chart, for neurodevelopmental screening as part of regular health check-ups by medical practitioners in rural Bangladesh is explored.

3.2 PAPER #3. *USE OF DEVELOPMENTAL MILESTONE CHART (DMC) IN RURAL BANGLADESH TO EDUCATE HEALTH WORKERS AND STIMULATE REFERRAL FOR EARLY DIAGNOSIS AND INTERVENTION*

BRIEF REPORT

Use of a Developmental Milestone Chart (DMC) in Rural Bangladesh to Educate Health Workers and Stimulate Referral for Early Diagnosis and Intervention

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ABSTRACT

We aimed to determine the feasibility of using a simplified Developmental Milestone Chart (DMC) for assessment of neurodevelopmental status of children of age ≥ 1 month and ≤ 8 years. Participants were assessed by medical practitioners using DMC as part of regular health checkups in three sub-districts in Bangladesh between January and May 2017. Total 256 children were recruited (41.0% girls, mean age 1.3 ± 1.6 years). Total 107 children (41.8%) failed at least one and 3 (1.2%) failed all four developmental milestones. Majority missed motor milestones (75.6%, $n = 81$). Four medical practitioners trained on the use of DMC deemed it to be an appropriate tool for developmental screening as part of regular health checkups/care in terms of acceptability, practicality and implementation. In countries with limited facilities, a simplified instrument such as the DMC can be administered by medical practitioners in rural settings. However, further studies are required to establish the validity of DMC before it could be adopted into routine clinical practices.

KEYWORDS: developmental screening; early diagnosis; Bangladesh; low- and middle-income country (LMIC); developmental milestones

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BACKGROUND

Advances in perinatal care have led to a marked increase in neonatal survival in low- and middle-income countries (LMICs) globally [1]. This is met by concerns of increased adverse neurodevelopmental outcomes [2], which is an emerging concern in countries such as Bangladesh where marked reduction in under-five mortality has been observed in the past decades [3]. Diagnosis of developmental disorders is delayed in part due to lack of awareness among health practitioners in LMICs [4].

Developmental milestones are useful predictors for neurodevelopment, which can enable early identification of disability [5, 6]. Several tools are being used to identify developmental delays. However, they are often extensive, restricted to certain age groups and have not been incorporated into routine clinical practice [7, 8].

We explored the feasibility of the use of the DMC to assess the childhood neurodevelopment as part of regular health checkups by medical practitioners and assessed the neurodevelopmental status of children in rural Bangladesh.

METHODS

This is a feasibility study on the application of a neurodevelopmental screening tool (i.e. DMC) by medical practitioners in rural settings. We followed Fischer *et al.* in a review describing the feasibility of the use of developmental screening tools at primary health-care level in low-and middle-income setting. In consultation with a group of international experts, the following characteristics were selected to assess feasibility: cost of the tool, access to application, training required, time to administer the tool, validity, reliability, results useful to guide action and results understood by caregivers and workers [9].

Children of age ≥ 1 month to ≤ 8 years were assessed by medical practitioners using the DMC in three subdistricts (Shahjadpur, Sirajganj and Manikganj Sadar) located in central and northern parts of Bangladesh between January 2017 and May 2017.

Medical practitioners underwent an hour-long training by the study investigators on the use of the DMC. The tool was administered in outpatient clinics as part of routine checkups. Extensive field notes and comments were collected from the medical practitioners on their experience in administering the DMC. Qualitative data were thematically analysed to determine whether the use of DMC as part of routine medical checkups is appropriate in terms of acceptability, practicality and implementation.

Acceptability reflected the extent to which DMC was considered appropriate [10]. Practicality implied the degree to which the DMC can be used with existing resources and implementation reflected the degree to which it can be used within existing contexts [11].

DMC summarizes age-specific representative milestones (see Supplementary Item 1 and Supplementary Item 2). In total, 50 representative milestones have been selected, modified and included in the DMC from the existing milestone charts and from field experience of health-care providers during previous trials in Cambodia [12–16]. The milestones are grouped into four domains: gross motor, fine motor, language and speech and social development. A translated Bengali version of the tool has been used for this study (see Supplementary Item 2).

Descriptive analysis (mean, median and proportion) was done by SPSS Statistics software version 23 (IBM Corporation, Chicago, Illinois, USA). Feedback from medical practitioners were documented as field notes and reflections, which were subsequently transcribed for further analysis.

This study has been approved by Bangladesh Medical Research Council Human Research Ethics Committee (HREC No. 08914122017) and the Asian Institute of Disability and Development Human Research Ethics Committee (southasia-irb-2017-l-03). Informed written consent was obtained from caregivers.

RESULTS

Neurodevelopmental status of the children

DMC was administered to 256 children as part of routine checkup by four medical practitioners. In total, 41.0% ($n = 105$) of the study participants were girls, and the mean age was 1.3 ± 1.6 years (median 9 months).

In total, 107 (41.8%) children failed at least one milestone, and 64 (25.0%) children failed at least two milestones. In total, 149 (58.0%) children achieved all milestones and 3 children (1.2%) failed all four milestones. Majority (61.7%, $n = 66$) of the

Table 1. Number of milestones failed and the number of children failed one or more milestones according to their age

Number of milestones failed	n (%)			
None	149 (58.2)			
At least 1	107 (41.8)			
At least 2	64 (25.0)			
At least 3	11 (4.3)			
All 4	3 (1.2)			

Age range	Study population	Children who missed milestone		
		Girl (%)	Boy (%)	Total (%)
1–3 months	25	9 (22.0)	8 (12.1)	17 (15.9)
4–6 months	57	9 (22.0)	19 (28.8)	28 (26.2)
7–9 months	51	5 (12.2)	16 (24.2)	21 (19.6)
10–12 months	26	2 (4.9)	4 (6.1)	6 (5.6)
13–15 months	22	4 (9.8)	6 (9.1)	10 (9.3)
16–18 months	20	5 (12.2)	4 (6.1)	9 (8.40
19–23 months	6	0 (0.0)	3 (4.5)	3 (2.8)
2–3 years	20	4 (9.8)	3 (4.5)	7 (6.5)
3–4 years	7	0 (0.0)	0 (0.0)	0 (0.0)
4–5 years	9	1 (2.4)	2 (3.0)	3 (2.8)
5–6 years	0	0 (0.0)	0 (0.0)	0 (0.0)
6–8 years	12	2 (4.9)	1 (1.5)	3 (2.8)
Total	256	41 (100.0)	66 (100.0)	107 (100.0)

children who failed milestones were between 1 and 9 months of age (Table 1).

In total, 81 (75.6%) children missed motor milestones. In total, 37 (34.6%) children missed milestones in the language and speech domain, and 35 (32.7%) children missed milestones in the social development domain.

Acceptability

The medical practitioners reported that administration of the tool provided information covering multiple areas of child development that was useful to them for referrals of early intervention and for anticipatory guidance. The tool was easy to interpret and communicate to the study participants, and there were no reported barriers to administration from them. Examples of their responses include:

'The tool is easy to administer and did not take long'

and,

'I am happy to use this routinely during outpatient consultation'

Administration required minimal time (<15 min); however, exact duration was not recorded.

Practicality

The DMC yields valuable information through a brief non-intrusive assessment. All four medical practitioners managed to integrate DMC into routine practice. Moreover, it is a single page tool for up to 8 years of age. Therefore, maintaining the DMC as part of routine medical records of children as they grow is not resource-intensive. However, there was comments made to "add pictures of age appropriate milestones in the form".

Implementation

One trained medical practitioner is required to administer the DMC, and there is no additional cost for administration of the tool as part of routine checkup. The medical practitioners deemed the DMC a helpful tool for timely referral of children for specialized care. It was additionally reported to be useful for training of health workers for establishment of suitable referral system, thereby feasible within the existing context.

DISCUSSION

We primarily aimed to see how DMC will be accepted by health practitioners and what information it may yield if implemented in a rural setting. There are few available tools that have been developed and validated for assessment of neurodevelopmental status of children by low skilled personnel in LMICs like Bangladesh [7]. Two studies conducted in Bangladesh assessed and reported neurodevelopmental status among children in urban and rural settings [7, 8]. However, these tools are extensive and have long administration time (~30–45 min).

The DMC in contrast is a comprehensive tool for developmental screening which is brief, easy to administer, and available in Bengali. We confirmed acceptability of the tool by medical practitioners and the felt need for such a tool in assisting them. Although further studies are required before the DMC could be adopted into routine clinical practices. It is also important to assess community practitioners' views on the use of the tool in subsequent studies to explore whether the DMC can serve as an educational resource for informing health-care workers regarding childhood development to facilitate early referral.

DMC shows some promise as a simple developmental screening tool for frontline health workers in LMICs. For example, it was previously used in Cambodia where it was deemed as a useful tool for continuous training in child development by encouraging health personnel to familiarize with normal milestones and alert them of deviances from the norm [12, 13].

Study limitations

One major limitation of the study is that this is an observational study, and no further follow up was conducted for the children who missed milestones. Further validation studies are needed for estimation of the sensitivity and specificity of the DMC in predicting neurodevelopmental outcomes. Moreover, we had to rely on opportunistic sampling which is not ideal, and the study tool has not been previously validated for local use. Data on time of administration were not collected as part of the study. Advanced statistical analysis was also limited by small sample size. Despite these limitations, we found that DMC is a useful tool for developmental screening. This study provides valuable insights for further exploration.

CONCLUSION

In countries with limited facilities, a simplified instrument such as the DMC can be administered by medical practitioners in rural settings. However, further studies are required to establish the validity of DMC before it could be adopted into routine clinical practices.

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3.3 CHAPTER SYNOPSIS

In this chapter, strategies for early detection of children with CP in low resouce settings have been explored. The use of the best practice tools for early detection to ensure early intervention is often lacking in low resource settings. The DMC has been identified as a suitable tool for developmental screening that could be incorporated into regular health checkups in low resource settings. It can serve as a valuable screening tool to ensure early referral for comprehensive assessment by a qualified clinician for an interim high risk of CP clinical diagnosis based on risk factors and clinical presentation and thereby facilitate early intervention within the period of optimal neuroplasticity.

Given the known importance of early intervention, we then explored the feasibility and outcomes of an early intervention program in a rural subdistrict of Bangladesh. The results of this trial are reported in the following chapter, Chapter 4.

8

CHAPTER 4. INTERVENTION FOR CHILDREN WITH CEREBRAL PALSY IN BANGLADESH

4.1 INTRODUCTION

Delayed diagnosis of CP limits early intervention within the period of optimum neuroplasticity of the developing brain. Although the benefits of early intervention for children with CP are apparent and evidence-based interventions for CP are available,(46) there is an overall dearth of evidence on the effect of interventions for children with CP in LMICs, such as Bangladesh. Caregiver led community-based rehabilitation programs are instrumental in an LMICs such a Bangladesh, where there is an overall lack of trained allied health workers.

In this chapter, the outcome of a community-based parent led early intervention and rehabilitation program for children with CP in rural Bangladesh is described.

4.2 PAPER #4. OUTCOME OF COMMUNITY-BASED PARENTS LED EARLY INTERVENTION FOR CHILDREN WITH CEREBRAL PALSY IN RURAL BANGLADESH: A QUASI-EXPERIMENTAL STUDY

Outcome of community-based early intervention and rehabilitation for children with cerebral palsy in rural Bangladesh: A quasi-experimental study

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Abstract: We aimed to evaluate the outcome of a community-based early intervention and rehabilitation for children with cerebral palsy (CP) in Bangladesh. Children registered into the Bangladesh CP Register (BCPR) were recruited in two groups for this study: Group A received a comprehensive six months long community-based caregiver-led intervention and rehabilitation program at the CSF "Shishu Shorgo" Rehabilitation and Early Intervention Centres developed to support participants from the BCPR. Group B received standard care. A quasi-experimental study was conducted. Data were obtained at baseline, end of program (i.e. 6 months), 12-month follow-up. Outcome measures included gross motor functional measure (GMFM-66), Communication Function Classification System (CFCS), Viking Speech Scale (VSS) of children and depression, anxiety, and stress scale (DASS 21) of primary caregivers. Between October-2016 and March-2017, 156 children with CP were recruited (77 in Group A and 79 in Group B). the total score of GMFM-66, CFCS level and VSS level significantly improved in Group A (*p*<0.05 for all), and deteriorated in Group B (p<0.001, p=0.095, p=0.232). The intervention showed promising outcomes particularly for children with CP under five years of age. There is a need for caregiver led community-based rehabilitation programs for children with CP in LMICs.

Keywords: Cerebral palsy; children; early intervention; community-based; low-and middle-income country; Bangladesh

1. Introduction

Cerebral palsy (CP) is the most common physical disability of childhood. The most recent and widely used definition of CP is "a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour; by epilepsy, and by secondary musculoskeletal problems" [1]. While the knowledge on the antecedents and preventive

strategies for CP has advanced considerably, our understanding of the prognosis of CP in terms of type and severity of everyday functioning, particularly in low resource settings, remains poorly understood.[2-4] Severity of brain lesions, age at the time of diagnosis and first rehabilitation, and access to evidence-based interventions are some of the important predictors of functional outcomes for children with CP.[5]

Recent studies from low and middle-income countries (LMICs) report a greater burden and severity of CP and associated impairments.[6-8] A population-based study in Bangladesh additionally reported delayed diagnosis at 5.2 years of age [6] beyond the period of optimum neuroplasticity of the developing brain.[9] Children with CP reach 90% of their gross motor potential within the first five years of life, and even earlier for those with severe CP.[10-12] Early intervention is therefore crucial for optimizing both motor and functional outcomes of children with CP. [13]

In addition to maximizing neuroplasticity and minimizing the detrimental modifications to muscle and bone growth, nutrition and development, outcomes of interventions for children with CP are strongly linked to caregiver wellbeing.[9,14] This has been evidenced in studies from LMICs including Bangladesh and Ghana.[14,15] Findings from a study in Zimbabwe also reported that caregivers of children with CP had poor health-related quality of life, high levels of depression, anxiety and stress, and felt overwhelmed by the economic burden and their caregiving role.[16]

Due to the heterogeneity of CP in terms of etiology, brain injury, severity of impairments and co-occurring conditions, children with CP have diverse needs which warrant a comprehensive rehabilitation program. These programs also need to address a range of medical, social and cultural barriers prevalent in rural and remote communities in LMICs.[17] A recent systematic review highlights the lack of evidence on efficacy for the majority of the interventions in use and the dire need for further research to address the existing research–practice gaps.[18] This is particularly true in LMICs such as Bangladesh where children with CP and their families are faced with numerous barriers in addition to those still prevailing in high income settings.[19]

Barriers to intervention for children with CP include a) delayed diagnosis of CP beyond critical window of neuroplasticity, b) poor or no access to evidence-based early intervention, c) inadequate state funded support and initiatives further propagating the disability and poverty cycle and widening the prevailing inequities, d) inability to afford services, e) poor accessibility due to lack of disability inclusive infrastructure and public transport systems, f) health workforce crisis particularly of allied health workers required to support children with CP and g) prevailing misconceptions, stigma and social exclusion. It is imperative that these factors are considered in the development of interventions with enhanced relevance for children with CP and their families in low resource settings.[6,17,19-22]

CSF Global (www.csf-global.org), an independent not-for-profit organization, committed to the establishment of a rights-based inclusive society for children with disability in LMICs, developed a comprehensive community-based caregiver-led intervention program for children with CP provided at the CSF "Shishu Shorgo" (Bengali title which translates to 'Children's Heaven') Rehabilitation and Early Intervention Centres in Bangladesh. This program was developed to support participants from the Bangladesh CP Register (BCPR). In this study, we aimed to evaluate the outcome of this

existing program for children with CP and their primary caregivers in a rural subdistrict of Bangladesh.

2. Materials and Methods

Study design, setting and participants

This was a pragmatic design quasi-experimental study conducted in a Northern sub-district of Bangladesh. The study participants included a subset of the BCPR study population. The BCPR is an ongoing surveillance of children (0–18 years) which includes children with CP from rural communities using a novel method of case ascertainment, the key informant method (KIM), followed by clinical confirmation of diagnosis of CP and data collection by a multidisciplinary team including assessment by a physician. The detailed study protocol and findings have been described in previous publications.[6,23]

The rehabilitation needs of the children are assessed and documented as part of the BCPR study. The CSF "Shishu Shorgo" rehabilitation centre's services were offered to all children with CP who had an identified need for therapy between October 2016 and March 2017. However, not all families were able to access these services due to personal or family circumstances.

The CSF "Shishu Shorgo" rehabilitation centres offers a six months program for children with CP with two intakes per year. Children enrolled at February and August 2016 intake (to be known throughout this manuscript as Group A) were recruited for this study. Additionally, data were collected on another group (to be known throughout this manuscript as Group B) of BCPR registrants who were not able to participate in the program. This group received standard care only, which consisted of basic advice provided by the BCPR team including physician and physiotherapist at the time of registration into the BCPR. Primary caregivers of all the children were also interviewed for assessment of their mental wellbeing. All assessments were conducted as part of the services provided at the CSF "Shishu Shorgo" Rehabilitation Centres for Group A. Assessments for Group B were conducted during home visits by an assistant physiotherapist trained in study procedures.

We collected outcome data on both groups during three time points; at baseline (prior to enrolment into the program), at the end of the program (i.e. 6 months) and follow-up at 12 months.

Intervention received by Group A

The program at CSF "Shishu Shorgo" serves the local community as the backbone for intervention for children with CP. It is a family centered program largely run by primary caregivers along with two community therapists (CT) in each center. The CTs are local community members who receive 15 days of structured training from a qualified physiotherapist on the provision of family centered rehabilitation services for children with disability and at least three months of supervised practice in a community rehabilitation centre before they lead a group under supervision of the training physiotherapist.

Twenty children were enrolled in each intake per centre, a morning group and afternoon group each with ten children. The children at CSF "Shishu Shorgo" undergo assessment and individual goal setting by the primary caregivers and the CT at enrollment. They attend three hourly sessions a day, five days a week at CSF "Shishu

Shorgo" centers. A manual (https://www.disabilityasia.org/parent-information) has been 141
developed to assist the CTs to run the early intervention program aimed at optimising 142
neurocognitive outcomes among children with CP in rural communities. It also promotes 143
participation of the children with CP in their family, school, and the community. This 144
"Shishu Shorgo" early intervention program is comprised of the following key 145
components, 146

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1. Group therapy: The group therapy focuses on the development of the following 148
skills: activities of daily living (toileting, dressing, eating), language and communication, 149
movement, cognition, and social skills. 150
2. Community follow-up: Throughout the six months long program, the CT provide 151
community follow up for each child and family. The goals of this community follow-up 152
are i) provision of strategies and assistive devices to assist the child at home with activities 153
of daily living (washing, toileting, eating, dressing), ii) supporting the child's local school 154
to enable their admission to school and participation in school activities, iii) increasing 155
awareness about disability and the child's abilities and rights to facilitate the child's family 156
and community develop support networks and increase opportunities for the child to 157
participate in the community, and iv) supporting the child to develop a meaningful 158
vocation in their family and community, particularly for those children unable to attend 159
school. 160
3. Primary caregiver training, peer support and education: The children attend the 161
sessions with at least one primary caregiver who is engaged in all elements of the program 162
to develop skills on day-to-day care of the children with CP using the CSF "Shishu 163
Shorgo" program manual. Parent support and education is provided through involving 164
the child's primary caregivers in all elements of the program. The CT involve the parent 165
in group therapy and community follow-up by providing family-centred care, keeping 166
the primary caregiver informed about the child's progress, and providing 167
recommendations and empowering primary caregivers to advocate for and facilitate their 168
child's participation in their home, community, school and vocation. Through this 169
program, the primary caregivers form support networks/peer group with other caregivers 170
of children with disabilities. 171

Intervention received by Group B 172
Group B did not opt for the rehabilitation at the CSF "Shishu Shorgo" Rehabilitation 173
Centres and received standard care i.e., no rehabilitation service aside from advice 174
provided by the multidisciplinary team at the BCPR camps during recruitment into the 175
register. 176

Outcome Measures assessed for both Groups A and B 177
The children and their primary caregivers were assessed at baseline at the time of 178
enrollment, after six-month period to measure the immediate outcome of the intervention 179
and after twelve months to evaluate long term effects of the intervention. A qualified 180
physiotherapist was trained by the study investigators on the assessments. The following 181
instruments were used for assessment of the children and their primary caregivers, 182

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1. Motor function: Gross Motor Function Measure (GMFM-66) and Gross Motor 184
Function Classification System (GMFCS) were used to evaluate changes in motor function 185
of the children with CP.[24,25] The GMFM is a criterion referenced assessment designed 186
and validated to measure change in gross motor function over time in children with CP. 187
GMFCS evaluates movement skills such as sitting, walking and use of mobility devices 188
and categorizes gross motor function into five levels. We reported and analyzed GMFCS 189

as ordinal and GMFM scores as continuous variables. GMFM-66 data was entered, stored, and analyzed using the Gross Motor Ability Estimator (GMAE-2) Scoring Software for the GMFM.[26]

2. Communication: Communication Function Classification System (CFCS), was used to classify the everyday communication of the children with CP into one of five levels according to effectiveness of communication which considers means of communication including speech, gesture, facial expression and augmentative and alternative communication.[27] A child classified at Level I is a more effective communicator than a child classified at Level V. We reported and analyzed CFCS as an ordinal variable.

3. Speech: Viking Speech Scale (VSS) is used to classify children's speech production, We reported and analyzed as an ordinal variable.[28]

4. Mental wellbeing of primary caregivers: Depression Anxiety Stress Scale (DASS-21), a 21 item self-report instrument, was used to measure - depression, anxiety and stress - of the primary caregivers of the children with CP.[29] The primary caregivers were asked to use 4-point severity/frequency scales to rate the extent to which they have experienced each state over the past week. DASS-21 scores were summed into 'depression', 'anxiety' and 'stress' scale and categorized as 'normal', 'mild', 'moderate', 'severe' or 'extremely severe' as per instrument protocol for analysis and interpretation. We reported and analyzed Depression, Anxiety and Stress scores as continuous variable for Friedman analysis.

Ethical considerations

Ethics approval for this study was obtained from the Bangladesh Medical Research Council (BMRC) (Ref: BMRC/NREC/2016-2019/469) and Asian Institute of Disability and Development (AIDD) (southasia-irb- 2016-1-07). Informed written consent was obtained from the primary caregivers of the children.

Statistical Analysis

Descriptive methods were used to summarize the cohort. Normality was checked using Shapiro-Wilk and visual inspection of the box plots. Normality assumptions failed therefore the non-parametric Friedman Test with post hoc pairwise comparisons was used and reported using median and Interquartile Range (IQR). However, data was also reported using the mean (SD) for clinical interpretation. There was a statistically significant difference between ages for Group A and Group B therefore we could not run any regression analysis using age as a covariate. Analysis was carried out using SPSS version 24 (IBM Corporation, Chicago, Illinois, USA). A p-value of <0.05 was considered significant.

3. Results

Between October 2016 and March 2017, 156 children with CP were recruited to the study (77 in Group A and 79 in Group B). Seventy-seven children with CP enrolled in the CSF "Shishu Shorgo" formed Group A and 79 children with CP who received standard care (i.e., basic rehabilitation education with no structured rehabilitation) formed Group B (mean (SD) age at baseline (i.e., 0 month), Group A vs Group B: 4.3 (2.9) vs 11.1 (4.0), p value<0.001. Post hoc analysis to investigate the age differences were performed and comparison within groups were also conducted where groups were not matched by age and sample size.

The demographic characteristics of the study participants are summarized in **Table 1.** The male-female ratio in Group A and Group B were 1.4:1 and 1.5:1 respectively (p=0.448). Both groups had similar sociodemographic characteristics; no significant (p>0.05) difference was observed between the groups in terms of type of accommodation, source of drinking water, sanitation, paternal education, and occupation. However, the median monthly family income and maternal educational level were significantly lower in Group B compared with Group A (*p*=0.005 and *p*=0.010 respectively).

Table 1. *Sociodemographic characteristics of the study participants*

Characteristic	Group A (n=77)	Group B (n=79)	*p*-value [b]
Age			
Mean (SD)	4.3 (2.9)	11.1 (4.0)	**<0.001[c]**
Median [IQR]	3.4 (2.4, 5.4)	11.6 (7.9, 14.1)	**<0.001[d]**
Sex			
Male	45 (58.4)	48 (60.8)	0.448[e]
Female	32 (41.6)	31 (39.2)	
Monthly family income (BDT)~ [USD] [a,f]			
Mean (SD)	9870.5 (6390.7) [~ 84.8 (75.3)]	8256.4 (6289.9) ~ 97.3 (74.1)	0.119[c]
Median [IQR]	8000.0 [6000.0, 10000.0] ~ 94.3 [70.7, 117.9]	6000.0 [5500.0, 8250.0] ~ 70.7 [64.8, 97.2]	**0.005[d]**
Monthly family income in BDT (USD) [a]			
Below 10,000 (below ~120)	49 (66.2)	60 (76.9)	0.052
10,000-19,999 (~120-241)	15 (20.3)	15 (19.2)	
20,000-29,999 (~241-361)	9 (12.2)	1 (1.3)	
30000 and above (~361 & above)	1 (1.4)	2 (2.6)	
Type of accommodation [a]			
Temporary shelter (jhupri)	0 (0.0)	2 (2.6)	0.240
Mud (kutcha) house	55 (74.3)	61 (78.2)	
Semi-permanent (semi-pucca) house	13 (17.6)	13 (16.7)	
Permanent brick (pucca) house	6 (8.1)	2 (2.6)	
Source of drinking water [a]			
Tap water	1 (1.4)	0 (0.0)	0.487
Tube well	73 (98.6)	78 (100.0)	
Sanitation [a]			
No toilet facility	2 (2.7)	1 (1.3)	0.816
Non-sanitary latrine	23 (31.1)	24 (30.8)	
Sanitary latrine	49 (66.2)	53 (67.9)	
Maternal education [a]			
Illiterate	20 (27.0)	40 (51.3)	**0.010**
Primary	26 (35.1)	24 (30.8)	
Secondary	22 (29.7)	11 (14.1)	
Higher secondary and above	6 (8.2)	3 (3.8)	
Maternal occupation [a]			
Agriculture worker	1 (1.4)	2 (2.6)	0.720
Garments worker/weaver/tailor	9 (12.2)	12 (15.4)	
Unemployed	64 (86.5)	64 (82.1)	
Paternal education [a]			
Illiterate	26 (35.1)	40 (51.3)	0.174
Primary	23 (31.1)	19 (24.4)	
Secondary	18 (24.3)	16 (20.5)	

Characteristic	Group A (n=77)	Group B (n=79)	*p*-value [b]
Higher secondary and above	7 (9.5)	3 (3.8)	
Paternal occupation [a]			
Agriculture worker	11 (15.1)	23 (30.3)	0.207
Daily wage earners	10 (13.7)	12 (15.8)	
Business	16 (21.9)	16 (21.1)	
Garments worker/weaver/tailor	24 (32.9)	19 (25.0)	
Others	11 (15.1)	5 (6.6)	
Unemployed	1 (1.4)	1 (1.4)	

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3.1 GROUP A

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GMFM Score

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The median GMFM total score significantly improved between baseline and 12 months (p<0.001) in Group A. Similar significant improvement was observed for children aged less than five years however, for children aged five years and more, the scores remained unchanged between baseline and 12 months (p=0.058).(Table 2 and 3)

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GMFCS Level

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Overall, 81.6% children had GMFCS level III-V at baseline, which reduced to 67.6% at 6 months and again increased to 83.7% at 12 months (p<0.001) (Table 2). When disaggregated by age, the GMFCS level significantly improved among children aged less than five years between 0 and 6 months (p<0.001), and then slightly deteriorated between 6 and 12 months (p<0.001). Whereas for children aged five years and above in this group, the GMFCS level remained similar between 0 and 6 months (p=0.285) and significantly deteriorated between 6 and 12 months (p=0.792) (Table 3).

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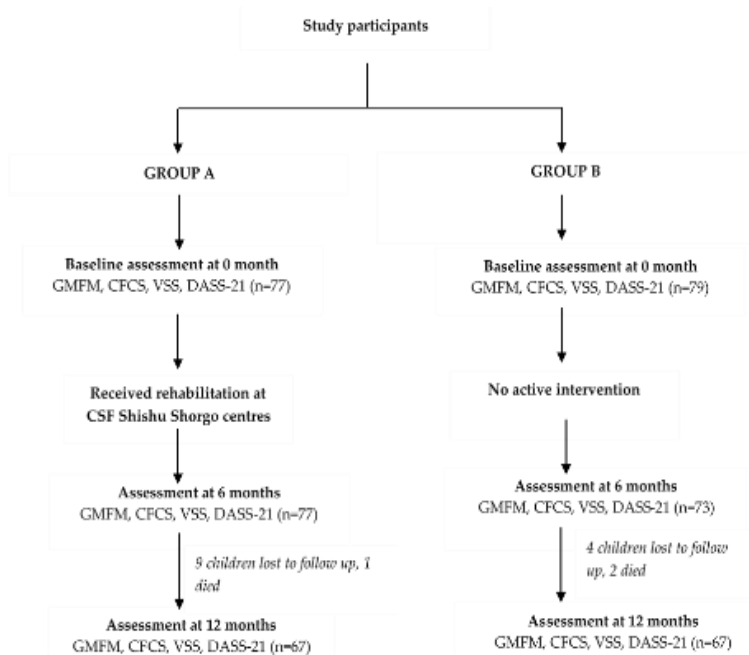
GMFM: Gross Motor Function Measure, CFCS: Communication Function Classification System, VSS: Viking Speech Scale, DASS-21: Depression Anxiety Stress Scale

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CFCS Level

Overall, the CFCS level significantly improved between baseline and 12 months of the study (p=0.002) (Table 2). Among the children aged less than five years, the proportion of children with CFCS level V reduced from 41.1% (n=23) to 24.5% (n=12) whereas, CFCS level I increased from 23.2% (n=13) to 26.5% (n=13) between baseline and 12 months (p=0.007). A similar less pronounced change was observed among the children aged five years and above (p=0.029) (Table 3).

VSS Level

Overall a significant improvement in VSS level was observed (p<0.001) (Table 2). Upon disaggregation by age, the children aged less than five years showed significant improvement between baseline and 6 months (p=0.041), 6 and 12 months (p<0.001), and baseline and 12 months (p<0.001). Whereas the children aged five years and above, showed a significant improvement between baseline and 6 months (p=0.014), followed by deterioration between 6 and 12 months (p=0.070); there was an overall significant change across all three time points (p=0.023) (Table 3).

Primary Caregiver DASS 21: Depression

At baseline overall 37.7% (n=29) of the caregivers had mild to extremely severe symptoms of depression. Although this percentage decreased to 19.7% (n=15) at 6 months of the study, we observed a marked increase (50.8%, n=34) in the proportion of caregivers with mild to extremely severe symptoms of depression at 12 months (*p*<0.001) (Table 2). These scores on depression subscale significantly improved among caregivers of children aged less than five years between baseline and 6 months (p<0.001), followed by a significant increase between 6 and 12 months (*p*<0.001. However, the overall change between baseline and 12 months was not significant. A similar pattern was observed for caregivers of children aged five years and above (Table 3). **Table 2.** Descriptive findings of the study participants

Timepoint	Group A				Group B			
	0 month	6 months	12 months	*p* value [a]	0 month	6 months	12 months	*p* value [a]
	n=77	n=77	n=67		n=79	n=73	n=67	
GMFM Total score								
Mean (SD)	32.5 (18.6)	42.2 (20.1)	42.3 (18.2)	-	39.3 (22.0)	46.4 (23.5)	41.2 (19.4)	-
Median (IQR)	34.8 [16.0, 46.5]	43.6 [23.6, 54.4]	44.6 [30.5, 52.3]	<0.001	46.9 [16.0, 59.3]	46.9 [26.3, 65.8]	42.2 [22.7, 54.6]	<0.001
GMFCS, n [%]	**76**	**77**	**67**		**79**	**73**	**67**	
Level I	4 (5.3)	11 (14.3)	5 (7.5)	<0.001	1 (1.3)	7 (9.6)	1 (1.5)	<0.001
Level II	10 (13.2)	14 (18.2)	6 (9.0)		22 (27.8)	20 (27.4)	12 (17.9)	
Level III	14 (18.4)	19 (24.7)	20 (29.9)		19 (24.1)	11 (15.1)	16 (23.9)	
Level IV	16 (21.1)	14 (18.2)	17 (25.4)		7 (8.9)	16 (21.9)	15 (22.4)	
Level V	32 (42.1)	19 (24.7)	19 (28.4)		30 (38.0)	19 (26.0)	23 (34.3)	

Timepoint	Group A				Group B			
	0 month	6 months	12 months	*p* value [a]	0 month	6 months	12 months	*p* value [a]
	n=77	n=77	n=67		n=79	n=73	n=67	
CFCS, n [%]					n=77 [b]			
Level I	15 (19.5)	24 (31.2)	16 (23.9)	0.002	20 (26.0)	29 (39.7)	19 (28.4)	0.095
Level II	12 (15.6)	7 (9.1)	8 (11.9)		11 (14.3)	5 (6.8)	6 (9.0)	
Level III	11 (14.3)	13 (16.9)	19 (28.4)		13 (16.9)	9 (12.3)	18 (26.9)	
Level IV	11 (14.3)	12 (15.6)	8 (11.9)		17 (22.1)	12 (16.4)	3 (4.5)	
Level V	28 (36.4)	21 (27.3)	16 (23.9)		16 (20.8)	18 (24.7)	21 (31.3)	
VSS, n [%]								
Level I	4 (5.2)	8 (10.4)	13 (19.4)	<0.001	15 (19.0)	28 (38.4)	20 (29.9)	0.232
Level II	6 (7.8)	7 (9.1)	11 (16.4)		13 (16.5)	0 (0.0)	6 (9.0)	
Level III	5 (6.5)	5 (6.5)	5 (7.5)		6 (7.6)	5 (6.8)	7 (10.4)	
Level IV	13 (16.9)	13 (16.9)	38 (56.7)		41 (51.9)	39 (53.4)	34 (50.7)	
NA [aged ≤4 years]	49 (63.6)	44 (57.1)	0 (0.0)		4 (5.1)	1 (1.4)	0 (0.0)	
DASS 21, n [%]								
Depression symptoms		n=76 [b]						
Normal	48 (62.3)	61 (80.3)	33 (49.3)	<0.001	73 (92.4)	53 (72.6)	31 (46.3)	<0.001
Mild	7 (9.1)	8 (10.5)	13 (19.4)		6 (7.6)	7 (9.6)	22 (32.8)	
Moderate	14 (18.2)	6 (7.9)	20 (29.9)		0 (0.0)	11 (15.1)	14 (20.9)	
Severe	3 (3.9)	0 (0.0)	1 (1.5)		0 (0.0)	2 (2.7)	0 (0.0)	
Extremely severe	5 (6.5)	1 (1.3)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Anxiety symptoms		n=76 [b]				n=72 [b]		
Normal	45 (58.4)	56 (73.7)	4 (6.0)	<0.001	79 (100.0)	28 (38.9)	3 (4.5)	<0.001
Mild	14 (18.2)	6 (7.9)	4 (6.0)		0 (0.0)	10 (13.9)	2 (3.0)	
Moderate	2 (2.6)	7 (9.2)	27 (40.3)		0 (0.0)	22 (30.6)	32 (47.8)	
Severe	9 (11.7)	3 (3.9)	26 (38.8)		0 (0.0)	10 (13.9)	20 (29.9)	
Extremely severe	7 (9.1)	4 (5.3)	6 (9.0)		0 (0.0)	2 (2.8)	10 (14.9)	
Stress symptoms		n=76 [b]						
Normal	35 (45.5)	54 (71.1)	10 (14.9)	<0.001	34 (43.0)	56 (76.7)	5 (7.5)	<0.001
Mild	19 (24.7)	10 (13.2)	34 (50.7)		32 (40.5)	11 (15.1)	37 (55.2)	
Moderate	10 (13.0)	9 (11.8)	23 (34.3)		13 (16.5)	5 (6.8)	18 (26.9)	
Severe	8 (10.4)	1 (1.3)	0 (0.0)		0 (0.0)	1 (1.4)	7 (10.4)	
Extremely severe	5 (6.5)	2 (2.6)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	

[a] Friedman test, [b] Missing data

Primary Caregiver DASS 21: Anxiety

Overall, 41.6% (n=32) caregivers showed signs of mild to extremely severe symptoms of anxiety at baseline which decreased to 26.3% (n=20) at 6 months followed by a sharp rise to 94.0% (n=63) at 12 months (p<0.001) (Table 2). Among caregivers of children aged less than five years, the median (IQR) of anxiety score slightly improved between baseline and 6 months (p=0.046) but it increased significantly between 6 and 12 months (p<0.001). Similar observation was made among caregivers of children aged five years and above (Table 3).

Primary Caregiver DASS 21: Stress

Overall, a substantial improvement in the scores of stress subscale of the caregivers was observed between baseline and 6 months, however, this was followed by a deterioration between 6 months and 12 months (p<0.001) (Table 2). The median (IQR) score on stress subscale reduced significantly between baseline and 6 months among the caregivers of children aged less than five years (p<0.001), and caregivers of children aged above five years (p=0.002). However, the score increased significantly between 6 and 12 months for both the groups (Table 3).

3.2 GROUP B

GMFM Score

The GMFM total score significantly deteriorated between baseline and 12 months among children in Group B (p<0.001). When disaggregated by age, the median GMFM total score deteriorated between baseline and 6 months among both children aged less than five years (p=0.600) and children aged five years and above (p<0.001). The pattern remained unchanged between 6 and 12 months (p=0.345 for children aged less than five years and p<0.001 for children aged five years and above) (Table 2 and Table 3).

GMFCS Level

Overall, significant deterioration in GMFCS level between baseline and 12 months was also observed for children in Group B (GMFCS level III-V at baseline vs 12 months: 71.0% vs. 80.6%; p<0.001). However, the changes were not significant for children aged less than five years (p=0.097) but significant for children aged five years and above (p=<0.001) (Table 2 and Table 3).

Table 3. GMFM 66 and GMFCS among children in Group A (n=77) and Group B (n=79) according to their age at baseline*
*including data for the children lost to follow up and the deceased

Time point	Group A aged less than 5 years			Group A aged 5 or more years			Group B aged less than 5 years			Group B aged 5 or more years		
	0m (n=56)	6m (n=56)	12m (n=49)	0m (n=21)	6m (n=21)	12m (n=18)	0m (n=7)	6m (n=6)	12m (n=6)	0m (n=71)	6m (n=67)	12m (n=61)
GMFM 66	n=56	n=56	n=49	n=21	n=21	n=18	n =7	n=6	n=6	n=71	n=67	n=61
Mean (SD)	31.1 (18.3)	42.1 (20.1)	41.6 (17.8)	36.6 (19.3)	42.6 (20.6)	44.0 (19.7)	34.2 (24.4)	36.7 (30.0)	31.5 (21.3)	40.1 (21.9)	47.3 (22.9)	42.1 (19.1)
Median [IQR]	30.2 [14.8, 46.0]	43.2 [24.8, 54.4]	46.1 [27.2, 52.4]	43.6 [17.8, 51.0]	44.5 [22.9, 59.1]	43.6 [29.0, 52.6]	36.0 [10.4, 58.6]	33.7 [11.1, 64.1]	29.8 [10.4, 50.2]	48.5 [16.0, 59.9]	47.7 [30.0, 66.7]	44.4 [24.0, 55.1]
p value	Across all three time points: **<0.001**, 0m - 6m: **<0.001**, 6m-12m: 0.068, 0m - 12m: **<0.001**			Across all three time points: 0.058, 0m - 6m: **0.009**, 6m-12m:0.492, 0m - 12m: 0.093			Across all three time points: 0.607, 0m - 6m: 0.600, 6m-12m: 0.345, 0m - 12m: 0.463			Across all three time points: **<0.001**, 0m - 6m: **<0.001**, 6m-12m: **<0.001**, 0m - 12m: 0.147		
GMFCS level*												
Level I	4 (7.3)	11 (19.6)	4 (8.2)	0 (0.0)	0 (0.0)	1 (5.6)	1 (14.3)	1 (16.7)	0 (0.0)	0 (0.0)	6 (9.0)	1 (1.6)
Level II	5 (9.1)	9 (16.1)	6 (12.2)	5 (23.8)	5 (23.8)	0 (0.0)	1 (14.3)	1 (16.7)	1 (16.7)	21 (29.6)	19 (28.4)	11 (18.0)
Level III	14 (25.5)	14 (25.0)	13 (26.5)	0 (0.0)	5 (23.8)	7 (38.9)	1 (14.3)	1 (16.7)	1 (16.7)	18 (25.4)	10 (14.9)	15 (24.6)
Level IV	8 (14.5)	10 (17.9)	13 (26.5)	8 (38.1)	4 (19.0)	4 (22.2)	1 (14.3)	0 (0.0)	1 (16.7)	6 (8.5)	16 (23.9)	14 (23.0)
Level V	24 (43.6)	12 (21.4)	13 (26.5)	8 (38.1)	7 (33.3)	6 (33.3)	3 (42.9)	3 (50.0)	3 (50.0)	26 (36.6)	16 (23.9)	20 (32.8)
p value	Across all three time points: **<0.001**, 0m - 6m: **<0.001**, 6m-12m: **<0.001**, 0m - 12m: 0.192			Across all three time points: 0.107, 0m - 6m: 0.285, 6m-12m:0.792, 0m - 12m: 0.776			Across all three time points: 0.097, 0m - 6m: 0.317, 6m-12m: 0.180, 0m - 12m: 0.102			Across all three time points: **<0.001**, 0m - 6m: **0.001**, 6m-12m: **<0.001**, 0m - 12m: 0.168		
CFCS level										n=69		
Level I	13 (23.2)	16 (28.6)	13 (26.5)	2 (9.5)	8 (38.1)	3 (16.7)	1 (14.3)	1 (16.7)	0 (0.0)	19 (27.5)	28 (41.8)	19 (31.1)

Time point	Group A aged less than 5 years			Group A aged 5 or more years			Group B aged less than 5 years			Group B aged 5 or more years		
	0m (n=56)	6m (n=56)	12m (n=49)	0m (n=21)	6m (n=21)	12m (n=18)	0m (n=7)	6m (n=6)	12m (n=6)	0m (n=71)	6m (n=67)	12m (n=61)
GMFM 66	n=56	n=56	n=49	n=21	n=21	n=18	n =7	n=6	n=6	n=71	n=67	n=61
Level II	4 (7.1)	4 (7.1)	3 (6.1)	8 (38.1)	3 (14.3)	5 (27.8)	0 (0.0)	0 (0.0)	1 (16.7)	11 (15.9)	5 (7.5)	5 (8.2)
Level III	7 (12.5)	10 (17.9)	14 (28.6)	4 (19.0)	3 (14.3)	5 (27.8)	1 (14.3)	2 (33.3)	2 (33.3)	12 (17.4)	7 (10.4)	16 (26.2)
Level IV	9 (16.1)	9 (16.1)	7 (14.3)	2 (9.5)	3 (14.3)	1 (5.6)	3 (42.9)	1 (16.7)	0 (0.0)	13 (18.8)	11 (16.4)	3 (4.9)
Level V	23 (41.1)	17 (30.4)	12 (24.5)	5 (23.8)	4 (19.0)	4 (22.2)	2 (28.6)	2 (33.3)	3 (50.0)	14 (20.3)	16 (23.9)	18 (29.5)
p value	Across all three time points: **<0.007**, 0m - 6m: **<0.001**, 6m-12m: 0.73, 0m - 12m: **<0.012**			Across all three time points: **0.029**, 0m - 6m: **0.011**, 6m-12m:0.083, 0m - 12m: 0.705			Across all three time points: 0.807, 0m - 6m: 0.564, 6m - 12m: 0.414, 0m - 12m: 0.705			Across all three time points: 0.110, 0m - 6m: 0.177, 6m-12m: **0.015**, 0m - 12m: 0.131		
VSS												
Level I	2 (3.6)	2 (3.6)	11 (22.4)	2 (9.6)	6 (28.6)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	15 (21.1)	28 (41.8)	20 (32.8)
Level II	1 (1.8)	3 (5.4)	6 (12.2)	5 (23.8)	4 (19.0)	5 (27.8)	0 (0.0)	0 (0.0)	1 (16.7)	13 (18.3)	0 (0.0)	5 (8.2)
Level III	1 (1.8)	2 (3.6)	2 (4.1)	4 (19.0)	3 (14.3)	3 (16.7)	0 (0.0)	1 (16.7)	2 (33.3)	6 (8.5)	4 (6.0)	5 (8.2)
Level IV	3 (5.4)	5 (8.9)	30 (61.2)	10 (47.6)	8 (38.1)	8 (44.4)	4 (57.1)	4 (66.7)	3 (50.0)	37 (52.1)	35 (52.2)	31 (50.8)
Not applicable	49 (87.5)	44 (78.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (42.9)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
p value	Across all three time points: **<0.001**, 0m - 6m: **0.041**, 6m-12m: **<0.001**, 0m - 12m: **<0.001**			Across all three time points: **0.023**, 0m - 6m: **0.014**, 6m-12m:0.070, 0m - 12m: 0.414			Across all three time points: 0.368, 0m - 6m: 0.180, 6m-12m: 1.000, 0m - 12m: 0.144			Across all three time points: **0.045**, 0m - 6m: **0.011**, 6m-12m: 0.197, 0m - 12m: 0.236		
DASS 21: Depression*				(n=20)								
Mean (SD)	4.9 (4.1)	2.3 (2.6)	5.3 (2.7)	5.9 (5.7)	2.3 (1.6)	4.7 (1.6)	2.6 (2.1)	0.8 (1.6)	5.7 (1.5)	2.4 (1.4)	2.8 (2.7)	4.8 (1.9)
Median [IQR]	4.00 [2.0, 7.0]	2.0 [1.0, 3.0]	5.0 [3.0, 8.0]	4.0 [2.0, 8.0]	2.0 [1.0, 3.7]	4.0 [3.7, 6.2]	3.0 [1.0, 4.0]	0.0 [0.0, 1.7]	5.0 [4.7, 7.2]	2.0 [2.0, 3.0]	2.0 [1.0, 4.0]	5.0 [3.0, 6.0]

Time point	Group A aged less than 5 years			Group A aged 5 or more years			Group B aged less than 5 years			Group B aged 5 or more years		
	0m (n=56)	6m (n=56)	12m (n=49)	0m (n=21)	6m (n=21)	12m (n=18)	0m (n=7)	6m (n=6)	12m (n=6)	0m (n=71)	6m (n=67)	12m (n=61)
GMFM 66	n=56	n=56	n=49	n=21	n=21	n=18	n =7	n=6	n=6	n=71	n=67	n=61
p value	Across all three time points: **<0.001**, 0m - 6m:**<0.001**, 6m-12m: **<0.001**, 0m - 12m: 0.189			Across all three time points: **0.016**, 0m - 6m: **0.003**, 6m-12m: **0.003**, 0m - 12m: 0.943			Across all three time points: 0.094, 0m - 6m: 0.197, 6m-12m: **0.042**, 0m - 12m: 0.072			Across all three time points: **<0.001**, 0m - 6m: 0.725, 6m-12m: **<0.001**, 0m - 12m: **<0.001**		
DASS 21: Anxiety*			(n=47)		(n=20)						n=66	
Mean (SD)	4.0 (3.9)	2.7 (3.1)	7.1 (2.2)	4.2 (4.8)	2.4 (3.6)	7.1 (2.5)	0.6 (0.5)	3.2 (3.8)	6.0 (2.2)	0.9 (0.9	4.9 (3.1)	7.2 (2.2)
Median [IQR]	2.5 [1.0, 5.0]	2.0 [0.0, 4.0]	7.0 [5.0, 9.0]	3.0 [1.0, 6.0]	1.0 [0.0, 2.7]	8.0 [5.5, 9.0]	1.0 [0.0, 1.0]	2.0 [0.0, 6.7]	7.0 [4.2, 7.2]	1.0 [0.0, 1.0]	5.0 [2.0, 7.0]	7.0 [5.0, 9.0]
p value	Across all three time points: **<0.001**, 0m - 6m: **0.046**, 6m-12m: **<0.001**, 0m - 12m: **<0.001**			Across all three time points: **0.004**, 0m - 6m: 0.102, 6m-12m: **0.006**, 0m - 12m: 0.093			Across all three time points: **0.022**, 0m - 6m: 0.144, 6m-12m: 0.173, 0m - 12m: **0.027**			Across all three time points: **<0.001**, 0m - 6m: **<0.001**, 6m-12m: **<0.001**, 0m - 12m: **<0.001**		
DASS 21: Stress*			(n=48)		(n=20)							
Mean (SD)	8.2 (3.9)	5.8 (3.7)	8.4 (2.6)	9.7 (4.1)	5.5 (3.6)	8.1 (3.1)	6.4 (3.0)	3.0 (2.8)	7.7 (1.4)	7.5 (2.5)	5.4 (2.9)	9.3 (3.0)
Median [IQR]	7.0 [5.0, 11.0]	5.0 [3.0, 8.0]	8.5 [7.0, 10.0]	9.0 [7.5, 11.5]	5.5 [3.0, 8.0]	8.5 [5.7, 11.0]	7.0 [3.0, 9.0]	2.0 [0.7, 6.2]	7.5 [6.7, 8.5]	8.0 [6.0, 9.0]	5.0 [4.0, 8.0]	9.0 [7.0, 12.0]
p value	Across all three time points: **<0.001**, 0m - 6m:**<0.001**, 6m-12m: **<0.001**, 0m - 12m: 0.608			Across all three time points: **0.010**, 0m - 6m: **0.002**, 6m-12m: 0.058, 0m - 12m: 0.382			Across all three time points: 0.066, 0m - 6m: 0.206, 6m-12m: 0.066, 0m - 12m: 0.136			Across all three time points: **<0.001**, 0m - 6m: **<0.001**, 6m-12m: **<0.001**, 0m - 12m: **0.009**		

CFCS Level

Overall, the CFCS level deteriorated between baseline and 12 months (p=0.095). Upon disaggregation by age, no significant difference was observed in CFCS levels among children aged less than five years. Among children aged five years and above the CFCS level deteriorated significantly between 6 and 12 months (p=0.015) (Table 2 and Table 3).

VSS Level

Overall, the VSS level slightly improved among children between baseline and 6 months but then deteriorated between 6 and 12 months, however, this change between these timepoints were not statistically significant (p=0.232). When disaggregated by age, slight improvement in VSS level was observed for children aged less than five years between baseline and 6 months (p=0.180), 6 and 12 months (p=1.00) and baseline and 12 months (p=0.144). Children aged 5 years and more showed improvement in VSS level between baseline and 6 months (p=0.011), however it slightly deteriorated between 6 and 12 months (p=0.197) (Table 2 and Table 3).

Primary Caregiver DASS 21: Depression

The proportion of caregiver with depressive symptoms gradually increased across the three timepoints (p<0.001). The score on depression subscale decreased between baseline and 6 months (p=0.197) and increased between 6 and 12 months (p=0.042) among caregivers of children aged less than five years. However, the median score remained unchanged between baseline and 6 months for caregivers of children aged five years and above (p=0.725) but significantly increased between 6 and 12 months (p<0.001) (Table 2 and Table 3).

Primary Caregiver DASS 21: Anxiety

The proportion of mild to extremely severe anxiety symptoms gradually increased between baseline, 6 and 12 months (p<0.001) among primary caregivers of children. When disaggregated by age of children, the anxiety score increased between baseline and 6 months (p=0.144) and between 6 and 12 months (p=0.173) among caregivers of children aged less than five years. However, among caregivers of children aged five years and above, the median anxiety score increased between baseline and 6 months (p<0.001) and 6 and 12 months (p<0.001) (Table 2 and Table 3).

Primary Caregiver DASS 21: Stress

The mild to extremely severe symptoms of stress decreased between baseline and 6 months but increased between 6 and 12 months (p<0.001) among the primary caregivers. The median stress score decreased between baseline and 6 months for both subgroups (p=0.206 for children aged less than

five years and p<0.001 for children aged five years and above). This was followed by an increase between 6 and 12 months in both age groups (p=0.066 and p<0.001 respectively) (Table 2 and Table 3).

3.3 Mortality

Three children died during the study period: one from Group A (male, age: 7.2 years) and two from group B (female, age: 10.2 years and male, age: 7.5 years). All three children had severe motor (GMFCS Level V), communication (CFCS level V) and speech impairment (VSS level IV). All three families were living below the poverty line and residing in mud houses. All three mothers were unemployed even though two of them had higher level of education compared to their husbands who were employed.

4. Discussion

To the best of our knowledge this is one of few studies to systematically examine the outcome of a community-based early interventional and rehabilitation program for children with CP in Bangladesh and similar economy countries. The intervention in the present study incorporated several key components to address some of the barriers to intervention in low resource settings.[6,17,19-22] It is therefore scalable and easily replicable in other parts of Bangladesh and similar settings in other LMICs. The intervention is provided free of cost and accompanied by transportation service. It is delivered by community health workers, therefore, sustainable in absence of highly skilled allied health workers. The intervention concurrently aims to empower the primary caregivers, to be able to continue therapy beyond the scope of the study and better equip them for the caregiving role of their child's lifelong condition. The intervention also includes initial goal setting for each child with the primary caregivers at the time of enrollment – this is best practice for CP due to the heterogeneous nature of the condition and it enables individualization of care for optimal outcomes.[30,31]

The children who received the intervention showed significant improvement in GMFM total scores in the first six months. This increment was sustained among children who were aged less than five years. However, although not statistically significant there was a decline observed among those who were aged five years and above. In contrast, among those who did not receive intervention a decline in the median GMFM scores was observed across the three timepoints. This decline was statistically significant for children ages five years or more. However, this could be due to the difference in sample size between the two subgroups. This finding in Group A contrasts to some extent, with what has been previously published on motor function trajectories of children with CP. With the exception of GMFCS V, children with CP typically continue to increase in GMFM scores until about 5-7 years and then reach a plateau. It is later in adolescence that decline in motor function for those GMFCS III-V occurs.

Studies have shown that motor function is strongly linked to the nutritional status and quality of life of children with CP in LMICs.[32,33] Findings from the Bangladesh Cerebral Palsy Register have shown that majority of children with CP in Bangladesh have severe chronic undernutrition.[32] Another study in Bangladesh reported that individuals with CP are at high risk of poor health-related quality of life and mental health problems.[33] Therefore, the intervention provided in the present study which resulted in improved motor outcomes additionally holds the potential for better nutritional outcomes and enhanced wellbeing among these children.

There was significant improvement in communication and speech among the children who received the intervention. Upon stratification by age, better outcomes were observed among children aged less than five years. This finding reinforces the importance of early intervention before five years of age. Meanwhile a different pattern was observed among the children who did not receive the intervention in Group B. Those who were under five years of age did not show any significant change in communication, while the children over five years of age deteriorated significantly over time. There was no significant change observed for speech in this group. However, interpretations should be made with caution as the sample size for children under the age of five years in this group was considerably smaller than those above five years of age (i.e. 7,6 and 6 vs 71, 67 and 61 at 0, 6 and 12 months respectively). These findings underpin the need for more trained speech therapist in countries like Bangladesh and the inclusion of speech therapy in early intervention programs.

In addition to the direct benefits for the children with CP, the intervention was seen to significantly improve the DASS scores of their primary caregivers from the intervention group. This potentially reflects the beneficial effects of peer to peer support through the formation of caregiver networks within the intervention program at CSF "Shishu Shorgo" rehabilitation centres. Having a child with CP impacts the entire family, particularly the mothers who bear the majority of the burden of caregiving. Cultural factors, misconceptions and stigma around disability add further to the plight of the mothers. Furthermore, 86% and 82% of mothers in group A and B were unemployed respectively. According to the World Bank data female unemployment rate in Bangladesh is ~6%. This marked difference is most likely owing to their primary caregiver role to their children with CP.

A study in Bangladesh reported that primary caregivers of adolescents with CP are at significantly higher risk of depression and stress compared to the caregivers of their peers without CP.(11) In recent times, there has been an increasing shift towards greater participation of primary caregivers in therapy for their children.(31, 32) Studies reported improved child and caregiver outcomes through this approach. However, caregiver mental wellbeing is crucial for them to effectively deliver such interventions.(33)

Several studies showed that interventions for children with CP can significantly improve parental wellbeing.(31) Our findings support the recommendations from a previous study conducted in Bangladesh which highlights the importance of supporting caregiver mental wellbeing when designing interventions for individuals with CP.(11) Furthermore, interventions including holistic measures for poverty alleviation and improvement of social and economic capital of the families can also potentially yield better functional outcomes for children with CP.(34)

Early diagnosis and intervention improve outcomes, particularly among children with mild CP.(12) However, children with severe CP, who also tend to have more severe associated impairments, may make smaller gains with intervention . Population-based surveillance in Bangladesh have found increased vulnerability to mortality with greater motor severity and more associated impairments.(35) This is consistent with the findings in our study where all three children who died during the study period had severe gross motor, communication and speech impairment. Moreover, all three families were living in impoverished conditions and their family income was below the poverty line. These findings highlight the relationship between health outcomes and social determinants of health and the importance of addressing the prevailing inequities to reduce needless deaths among children with CP.

Study limitations

One of the major limitations of the study was that Group A and the Group B were significantly different in terms of age (mean age: 3.7 vs 9.6 years) which inhibited the statistical analysis; there was also variation in the baseline status of their motor and communication functions. These factors may have collectively influenced the study findings. There was also bias introduced due to the method of recruitment of study participants. The intervention was offered to all children with CP in need of therapy identified through the BCPR during the study period. Those who were able to take-up the provided intervention formed Group A, whereas, the families that were unable to take this opportunity due to personal or family circumstances formed Group B. Therefore, interpretation of the differences in outcome between the two groups should be made with caution considering that there are several differences between the children who received the intervention and those who did not including their age and severity of impairments at baseline. Yet, Group A and Group B did not show significant differences across most demographic characteristics and both groups showed short term improvement in motor outcomes.

The improvement among the children in Group B could possibly be due to the primary caregiver education provided at the time of registration in the BCPR; the registered children are also ensured access to assistive devices and have access to weekly physiotherapy clinics in the surveillance area. It could additionally be due to attrition bias as some of the more severe cases were lost to follow up or died during the study period. Moreover, the

heterogeneous nature of CP poses a challenge in the application and evaluation of interventions. Further exploration through large scale randomized controlled trial using the BCPR as the sampling frame to evaluate whether the beneficial effects of the intervention are sustained over long-term can generate more robust population level evidence.

Despite these limitations, this study was based on a population-based cohort (unlike institutional cohort subject to selection bias) and therefore represents the true nature and likely outcomes of community based and intervention programs in LMICs. As a pragmatic quasi experimental study, findings from this study including our reported limitations can inform clinicians and researchers in developing more holistic programs and well-designed experimental studies including randomized controlled trials.

5. Conclusions

The intervention in the present study has resulted in promising outcomes, particularly for young children with CP under five years of age. There is a need for such caregiver led community-based rehabilitation program for children with CP in LMICs such as Bangladesh, particularly in the rural settings, where services and trained health workers are scarce. This will ensure access to services to one of the most marginalized populations and promote optimal use of the limited resources. This work can potentially underpin the development of a sustainable model for rehabilitation of children with CP which can be scaled up in low resource settings.

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4.3 CHAPTER SYNOPSIS

In this chapter, the outcome of a community-based parent led early intervention program was assessed. The intervention demonstrated promising outcomes, particularly for children with CP under five years of age. However, further research is needed to assess the broader implications for scale in Bangladesh and other low resource settings.

The first four chapters of this thesis have involved an exploration of epidemiology, early detection, and early intervention in a LMIC, Bangladesh. This research has used the BCPR as a data resource and a sampling frame for clinical research. However, in most LMIC regions, there are no equivalent CP registers to allow enhanced understanding of the clinical characteristics and inform the development of intervention and rehabilitation programs. Therefore, in the following chapter of this thesis, we shift our focus to an alternative method for understanding children with CP. A hospital-based surveillance program was instituted in Vietnam. In chapter 4, results from this program regarding the clinical characteristics and nutritional status of children with CP in Vietnam will be described.
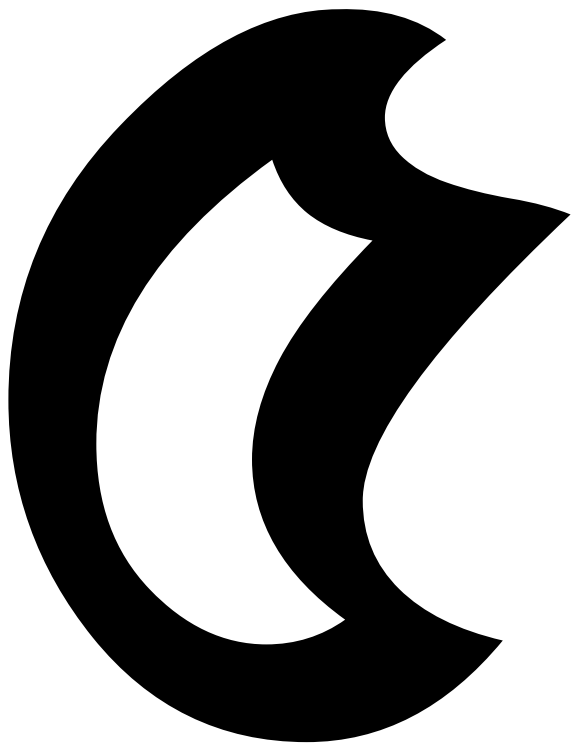
CHAPTER 5. HOSPITAL-BASED SURVEILLANCE OF CHILDREN WITH CEREBRAL PALSY IN VIETNAM

5.1 INTRODUCTION

The BCPR demonstrated what can be achieved with a CP register in a LMIC. Surveillance for children with CP is imperative in other LMICs where similar research and service gaps exist.

Upon commencement of my doctoral studies in July 2018, I relocated to Sydney. I had the opportunity to work with Professor Elizabeth Elliott and a team in Vietnam. This enabled the extension of my lessons and experience from the BCPR study to Vietnam. This new work would help us support the establishment of CP registers in multiple LMICs which could then collaborate with each other and with those from HICs.

A hospital-based surveillance of children with CP in Vietnam is described in this chapter. The protocol for the surveillance has been previously published.(42) This study enabled exploration of the clinical characteristics, etiology, rehabilitation, educational and nutritional status of children with CP in Vietnam. These findings have been described in the following publications.

5.2 PAPER #5 DATA ON CEREBRAL PALSY IN VIETNAM: FINDINGS FROM PROSPECTIVE HOSPITAL-BASED SURVEILLANCE IN VIETNAM

5.3 Paper #6. NUTRITIONAL STATUS OF CHILDREN WITH CEREBRAL PALSY: FINDINGS FROM PROSPECTIVE HOSPITAL-BASED SURVEILLANCE IN VIETNAM

Data on cerebral palsy in Vietnam will inform clinical practice and policy in low and middle-income countries

Tasneem Karim , Rachael Dossetor , Nguyen Thi Huong Giang , Trinh Quang Dung , Tran Vinh Son , Nguyen Xuan Hoa , Nguyen Hong Tuyet , Nguyen Thi Van Anh , Cao Minh Chau , Nguyen Van Bang , Nadia Badawi , Gulam Khandaker & Elizabeth Elliott

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ORIGINAL ARTICLE

Data on cerebral palsy in Vietnam will inform clinical practice and policy in low and middle-income countries

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ABSTRACT

Purpose: To document known risk factors, clinical severity, associated impairments and rehabilitation status of children presenting with cerebral palsy (CP) to the National Children's Hospital (NCH) in Hanoi, Vietnam.

Materials and methods: Active prospective ascertainment of cases of CP presenting between June and November 2017 to the NCH using surveillance modelled on the Paediatric Active Enhanced Disease Surveillance system in Australia.

Results: Data were collected on 765 children with CP (mean age: 2 years 7 months (SD 2 y 6 mo). Mean age at diagnosis was 1 year 8 months (SD 1 y 9 mo). Children predominantly had spastic CP (95.2%, $n = 729$), most were quadriplegic (69.6%, $n = 532$) and 60.3% ($n = 454$) were Gross Motor Functional Classification System level III-V. Of the children 76.2% ($n = 583$) had one/more associated impairments. 36.3% ($n = 276$) had presumed perinatal asphyxia, 26.5% ($n = 202$) were preterm. Physiotherapy (94.3%, $n = 663$) was the most common form of intervention used. Only 2.6% ($n = 12$) of the children who would have benefitted from assistive devices had wheelchairs.

Conclusion: We established hospital-based surveillance of CP in Hanoi and confirmed a high burden and severity of CP with potentially preventable risk factors. These data will inform clinician training and health policy and identify need for evidence-based care and assistive devices.

➤ IMPLICATIONS FOR REHABILITATION

- We identified a high number of children with severe forms of cerebral palsy (CP) in Hanoi, Vietnam through hospital-based surveillance.
- There is an urgent need for clinician training and access to and use of evidence-based interventions including assistive technology.
- This study will inform local capacity building and health policy for improved diagnosis and care of children with CP in Vietnam and other low and middle-income countries.

Introduction

Cerebral palsy (CP) is a group of disorders resulting from an insult to the developing brain and characterised by permanently disordered movement, co-ordination, balance or posture. Children with CP often have associated impairments including problems with development, vision, speech, cognition, epilepsy and feeding. CP is the leading cause of physical disability and data from high-income countries (HICs) show that the pooled prevalence is 2.9 per 1000 children, CP affects 2.1 per 1000 live births [1].

The prevalence of CP in Europe decreased from 1.9 to 1.8 per 1000 live births between 1980 to 2003 [2]. Recent findings from the Australian CP Register (ACPR) showed a decline in rates from 2.1 in 1995–1997 to 1.4 children per 1000 live births/neonatal survivors in the 2010–2012 period [3]. The decline in CP rates and severity in the HICs is the cumulative result of the impact advances in maternal and child health care and robust public health initiatives, guided by empirical evidence [3]. Furthermore, there are probably additional factors affecting CP prevalence that are not

yet identified. Neuroprotective approaches (e.g., administration of magnesium sulphate to mothers at risk of a preterm birth) and innovation in perinatal practice (e.g., cooling or induced mild hypothermia to reduce the impact of brain injury) are the key to the reducing the burden of CP, particularly due to known preventable risk factors, and multidisciplinary care is crucial to improving health and quality of life [4,5]. These interventions are often unavailable in low and middle-income countries (LMICs). Data are limited, particularly on trends, and there is no evidence of declining rates of CP in LMICs.

Service delivery for CP is seen as a public health priority by the Ministry of Health in Vietnam, however the lack of epidemiological data limits an evidence-based approach [6]. There is an urgent need for surveillance systems to collect local data to inform diagnoses, intervention and health policies in Vietnam. Furthermore, comprehensive pooled data from LMICs will inform regionally applicable strategies and models of care for children with CP and ensure optimal use of limited resources.

We aimed to identify children with CP at the National Children's Hospital (NCH), describe their demographic data and the aetiology, motor function, clinical severity, associated impairments, and rehabilitation status associated with CP. These data will form the basis of a national CP register in Vietnam.

Materials and methods

We established a method for active, hospital-based surveillance to identify children with CP, modelled on the Paediatric Active Enhanced Disease Surveillance (PAEDS) system operating in Australia [7]. Active, prospective case finding involves identification of cases on a daily basis as they come to the National Children's Hospital. Dedicated, trained clinicians at the hospital are responsible for actively seeking children with CP and collecting data using a standardised record form following thorough clinical assessment, history taking and review of existing medical records. Additional methodological details can be found in our study protocol and other publications [6,7].

Study site and participants

NCH is an 1800 bed tertiary paediatric hospital in Hanoi that provides services for about 100 000 inpatients and 1 million outpatients each year. The rehabilitation department sees approximately 80 to 100 children per day.

Baseline case identification by Vietnamese paediatricians took place between June and November 2017. Participants were children aged less than 18 years, who attended the rehabilitation department at NCH and were diagnosed with CP, according the definition used by the Surveillance of Cerebral Palsy in Europe and the Australian Cerebral Palsy Register (ACPR) [2,3]. Diagnosis of CP was confirmed by the paediatricians based on clinical assessment, history taking and review of existing hospital records and investigations using our study protocol and hospital guidelines. The definition, inclusion and exclusion criteria used for CP are described in the protocol for this study [6].

Detailed assessment and data collection

The questionnaire used for data collection is a modified version of the ACPR record form which was used for the Bangladesh CP Register (BCPR) Study [3,5]. The clinical information was collected by trained Vietnamese paediatricians at the National Children's Hospital. Some information provided in the questionnaire came from existing medical records. Responses were recorded in Vietnamese and translated into English by two of the investigators. Translated data were entered into a database by study investigators.

Sociodemographic details were collected. Families living on an average income of less than or equal to 653 000 Vietnam Dong (VND) per person, per month were defined as living below the poverty line [8].

Data were collected on the perinatal period as was clinical information including the age of CP diagnosis, presumed timing of injury causing CP and type of CP. The Gross Motor Function Classification System (GMFCS) and Manual Ability Classification System (MACS) were used to assess functional severity. MACS was determined for children over 4 years of age [9,10]. MRI scans were performed in some children and anthropometric measurements were documented to assess the nutritional status of the children and these data have been reported separately.

The presence and severity of associated impairments were documented based on clinical history, detailed assessment conducted by clinicians and report by the parents/primary caregivers.

Diagnosis of epilepsy was based on a clinical history of one or more unprovoked seizures in the previous 3 months beyond the neonatal period. An EEG assessment was done, clinical history was taken and relevant medical records were reviewed.

Intellectual impairment or delayed cognitive development was determined by clinicians based on clinical history and assessment or report by the parents/primary caregivers or review of medical records.

Visual impairment was determined through history, available medical records and clinical assessment of visual acuity and functional vision including counting fingers, hand motion and light perception. The monocular cover-uncover test was conducted to identify strabismus.

Assessment of hearing impairment was based on hearing-related medical history, including the child's response to name-call, clap and vehicle horns; previous ear infections, symptoms of ear pain or purulent drainage; family history; prescription and use of over-the-counter ototoxic medication; and previous hearing loss interventions. Otoscopic examination was performed to evaluate the pinna, external auditory canal, and tympanic membrane for any conditions that could be contributing to hearing loss or that may require further evaluation and treatment. Audiology was not performed.

Assessment of speech was based on the history taken from the primary caregiver and speech and language assessment by a medical practitioner. Expressive and respective language, naming quality, and quality of conversational speech were also observed.

Perinatal asphyxia was defined as a newborn failing to cry at the time of birth, experiencing delayed onset of breathing (>1min), or requiring assistance to initiate breathing.

Early feeding difficulty was recorded when a neonate was unable to feed in the first month of life due to poor sucking abilities.

Ethical considerations

Ethics approval was obtained from the University of Sydney Human Research Ethics Committee (HREC) (2016/456), Hanoi Medical University (HMU) (1722/QD-QHYHN) and the NCH in Hanoi (812/QD-BVNTU). Informed consent was obtained from parents or caregivers of all the study participants.

Statistical analysis

Data were checked for missing data and cleaned. We performed descriptive analyses (mean, standard deviation (SD), median and proportion). All analyses were performed using SPSS Statistics software version 24 (IBM Corporation, Chicago, Illinois, USA).

Results

Data were collected between June and November 2017 on 765 children with a clinical diagnosis of CP. The mean age of participants was 2 years 7 months (SD 2 y 6 mo; range: 2.4 mo–13y 5 mo), 64.2% were male ($n = 491$). The mean age at diagnosis of CP was 1 year 8 months (SD 1 y 9 mo).

Of the children, 90.2% ($n = 533$) were from the majority ethnic group in Vietnam, Kinh. Most (94.4%, $n = 711$) of the cohort were living in houses with finished floors. Sources of drinking water predominantly included piped water (55.6%, $n = 423$) and well water (37.3%, $n = 284$). Most (83.4%, $n = 633$) had a flushing toilet. The mean monthly income of families was 113.2 USD (SD 106.0 USD; range: 4.4–1565.2 USD). In total, 68.8% ($n = 501$) of families were living below the poverty line.

The mean maternal age was 26 years 10 months (SD 5 y 2.2 mo; range: 12 y 7.2 mo–45y 10.8 mo). Over a third of mothers (42.4%, $n = 323$) and fathers (40.5%, $n = 301$) had completed higher secondary education. However, 35.0% ($n = 266$) of mothers and 24.5% ($n = 183$) of fathers were unemployed. Detailed demographic characteristics are outlined in Table 1.

CP motor type and severity

The majority of children (95.2%, $n = 729$) were diagnosed with spastic CP, of whom 73.0% ($n = 532$) had quadriplegia, 21.5% ($n = 157$) had monoplegia/hemiplegia and 5.5% ($n = 40$) had diplegia. According to GMFCS, 60.3% ($n = 454$) were level III-V. Among these children who would have benefitted from assistive devices only 2.6% ($n = 12$) of them had access to a wheelchair. Of the 150 children over 4 years of age 22.0% ($n = 33$) had MACS level III-V (Table 2).

Associated impairments

Of the children, 76.3% ($n = 583$) had one or more associated impairments: 59.1% ($n = 450$) had speech impairment recorded by clinicians (including 258 children who were non-verbal), 57.8% ($n = 439$) had intellectual impairment, 1.7% ($n = 13$) had hearing impairment (including 3 children with bilateral deafness), 5.5% ($n = 41$) had visual impairment (including one child with functional blindness) and 10.8% ($n = 82$) had epilepsy (Table 2).

Risk factors

Over half (55.2%, $n = 416$) of the children had a prenatal or perinatal risk factor reported, 13.0% ($n = 98$) had a postnatal risk factor and the timing of the brain injury was unknown for 31.7% ($n = 239$). Potentially preventable risk factors including presumed perinatal asphyxia (36.3%, $n = 276$), neonatal jaundice (10.7%, $n = 81$), infection (9.1%, $n = 69$), brain haemorrhage (1.4%, $n = 11$) and traumatic/accidental brain injury (1.4%, $n = 11$) were reported (Table 3).

Of the mothers, 1.8% ($n = 13$) had assisted conception, 86.5% ($n = 652$) received regular antenatal care and 4.1% ($n = 31$) did not receive any antenatal care. Maternal complications during childbirth were reported in 23.1% ($n = 170$). The majority (90.8%,

$n = 687$) of children were born in hospital and 66.7% ($n = 504$) of births were by spontaneous vaginal delivery (Table 3). Of the 4.2% ($n = 31$) multiple births, 8 resulted from assisted conception (5 in vitro fertilisations, 1 artificial insemination, 1 gamete intrafallopian transfer and 1 ovulation stimulation).

The mean GA at birth was 37.2 weeks (SD 4.5wks; range: 25–43wks): 26.5% ($n = 202$) were born preterm (<37wks) of whom 37.6% ($n = 76$) were very preterm (28–31wks). The mean birthweight was 2783.0 grams (SD 708.0 g) and 26.3% ($n = 200$) of children were low birthweight (<2500 g). Of the 168 children 22.6% had early feeding difficulties.

In total, 85.5% ($n = 460$) of the cohort required a hospital transfer in the neonatal period: 27.8% ($n = 128$) were transferred to the only national central level hospital i.e., NCH, 49.1% ($n = 226$) to a provincial level hospital and 23.0% ($n = 106$) to a district level hospital. Over half (53.7%, $n = 411$) of the children received only routine care, however, 31.6% ($n = 242$) were treated in the neonatal intensive care unit and 5.6% ($n = 43$) received special care (Table 3).

Birth defects were reported in 14.8% ($n = 112$) including cardiovascular defects in 29 children. An MRI head scan was performed in 56.1% ($n = 424$) and reports were available for 36.1% ($n = 273$). A variety of structural anomalies and insults were identified. These data are currently being analysed and will be reported in detail elsewhere.

Immunisation

Of the children, 82.7% ($n = 623$) were fully vaccinated as per the national immunization schedule recommended for children in Vietnam and 94.0% ($n = 701$) had a BCG vaccine mark [11]. Of the children over 9 months of age and therefore eligible, 72.9% ($n = 373$) received the Measles-Rubella (MR) vaccine during the 2015 National MR campaign (Table 4).

Education and rehabilitation

Of the 75 children over 6 years of age who are eligible to attend school, 30.7% ($n = 23$) do not attend school and only 1.2% ($n = 9$) attend a special school. All the parents of children who received no form of rehabilitation reported that they were unaware of available therapies. Among the 92.6% ($n = 703$) who received rehabilitation, 94.3% ($n = 663$) received physiotherapy (however, no standard early intervention protocol was followed), 21.5% ($n = 151$) received advice and 0.7% ($n = 5$) underwent surgery. Only 11.5% ($n = 81$) had used an assistive device which rarely included a wheelchair or walker. Five children received treatment with muscle relaxants, and one received acupuncture (Table 4).

Discussion

We established an ongoing hospital-based surveillance system enabling collection of robust data which can guide health service planning, capacity building of health professionals and family support. The PAEDS mechanism is efficient, low cost and suitable for a hospital such as NCH [7]. It could be scaled up to hospitals across Vietnam and is the first step towards the establishment of a national CP register. It could additionally be used to monitor other conditions of public health importance as demonstrated in Australia [7,12].

Global collaborative initiatives in cerebral palsy research have been established in HICs. For example, the Surveillance of Cerebral Palsy in Europe was established in 1998 as a

Table 1. Demographic characteristics and living conditions of children and families.

Characteristics	n (%)
Ethnic group (n = 591)	
Majority group Kinh	533 (90.2)
Minority group Khac	58 (9.8)
Region (n = 756)	
Red River Delta	421 (55.7)
Northeast	146 (19.3)
North Central	115 (15.2)
Northwest	65 (8.6)
Central Highlands	6 (0.8)
Southeast	2 (0.3)
Mekong River Delta	1 (0.1)
South Central Coast	0 (0.0)
Mean parental age at time of birth (years) and range	
Mother (n = 764)	26.9 ± 5.2; 12.6–45.9
Father (n = 755)	30.2 ± 5.8; 16.2–56.9
Education level of mother (n = 762)	
Illiterate	2 (0.3)
Primary	36 (4.7)
Secondary/higher secondary	518 (68.0)
Graduate/post-graduate	130 (17.1)
Diploma/other trade qualification	76 (10.0)
Education level of father (n = 743)	
Illiterate	1 (0.1)
Primary	35 (4.7)
Secondary/higher secondary	522 (70.2)
Graduate/post-graduate	128 (17.2)
Diploma/other trade qualification	57 (7.7)
Primary carer (n = 596)	
Parent(s)	495 (83.1)
Grandparent(s)	62 (10.4)
Parent(s) and grandparent(s)	37 (6.2)
Other	2 (0.3)
Mean (± SD) number of household members and range	4.7 ± 1.3; 2–10
Mean (± SD) number of rooms per house and range	2.5 ± 1.2; 1–10
Source of drinking water (n = 761)	
Piped water	423 (55.6)
Well water	284 (37.3)
Other sources (pond, river, lake)	54 (7.1)
Sanitation (n = 759)	
Flush toilet	633 (83.4)
Pit toilet	126 (16.6)
Flooring type (n = 753)	
Finished floor	711 (94.4)
Rough wood/bamboo	29 (3.9)
Earth/sand	13 (1.7)
Monthly family income (n = 728)	
VND	
Mean ± SD	2 603 287.2 ± 2 436 897.5
Range	100 000–36 000 000
USD	
Mean ± SD	113.2 ± 106.0
Range	4.4–1565.2
Families living below the poverty line	501 (68.8)

Parents Occupation [38]	Mother (n = 760)	Father (n = 746)
Unemployed	266 (35.0)	183 (24.5)
Elementary occupations	244 (32.1)	279 (37.4)
Professional	148 (19.5)	94 (12.6)
Service and sales workers	29 (3.8)	69 (9.2)
Craft and related trade workers	23 (3.0)	22 (2.9)
Clerical support workers	15 (2.0)	12 (1.6)
Managers	15 (2.0)	1 (0.1)
Armed forces occupations	4 (0.5)	6 (0.8)
Plant and machine operators and assemblers	1 (0.1)	17 (2.3)
Technicians and associate professionals	0 (0.0)	52 (7.0)
Other	15 (2.0)	11 (1.5)

collaboration of professionals and researchers working with CP registries across Europe [2]. Such initiatives have only recently been explored in LMIC. In this paper we cite evidence from Bangladesh and Indonesia collected by the authors of this paper [5], which also use a modified version of the ACPR record form for data collection, enabling comparison of study findings. We will also be able to compare data collected in our study with that collected through the Surveillance of Cerebral Palsy in Europe [2]. However, comparisons must be made with caution due to disparities resulting from methodological differences.

Table 2. Baseline characteristics, predominant CP subtype, functional motor severity classifications and associated impairments of children with CP.

	n (%)
Sex (n = 765)	
Male	491 (64.2)
Mean (± SD) age of assessment at NCH (years)	2.6 ± 2.5
Age group (n = 765)	
<1	201 (26.3)
1 to <2	224 (29.3)
2 to <5	219 (28.6)
5 to <10	101 (13.2)
10 to <15	20 (2.6)
Mean (± SD) age of diagnosis of CP (years)	1.7 ± 1.8
Presumed timing of injury causing CP (n = 753)	
Pre and perinatal	416 (55.2)
Postnatal	98 (13.0)
Unknown	239 (31.7)
Type of CP (n = 765)	
Spastic	729 (95.3)
Quadriplegia	532 (69.6)
Monoplegia/hemiplegia	157 (20.5)
Diplegia	40 (5.2)
Triplegia	–
Dyskinetic	35 (4.6)
Ataxic	1 (0.1)
Hypotonic	–
GMFCS level (n = 754)	
I	179 (23.7)
II	121 (16.0)
III	103 (13.7)
IV	131 (17.4)
V	220 (29.2)
MACS level (n = 150)[a]	
I	55 (36.7)
II	62 (41.3)
III	21 (14.0)
IV	11 (7.3)
V	1 (0.7)
Associated impairments[b]	
One or more associated impairment(s) (n = 764)	582 (76.2)
Epilepsy (n = 758)	82 (10.8)
Speech impairment (n = 761)	449 (59.0)
Intellectual impairment (n = 759)	439 (57.8)
Strabismus (n = 452)	49 (10.8)
Visual impairment (n = 743)	40 (5.4)
Hearing impairment (n = 759)	13 (1.7)
Swallowing difficulty (n = 750)	60 (8.0)
Gastro-oesophageal reflux disease (GORD) (n = 748)	21 (2.8)

Data are n (%). MACS: Manual Ability Classification System; GMFCS: Gross Motor Function Classification System.
[a]MACS was applicable for 169 children ≥ 4 years.
[b]Multiple impairments were reported for several children.

Although data from LMICs are scarce, recent studies show that the burden of CP is substantially higher than in HICs. Population-based prevalence of 3.4 per 1000 children was reported in Bangladesh and 2.9 per 1000 children in Uganda [5,13]. In contrast, a study predominantly including HICs reported the overall worldwide prevalence of CP is 2.1 per 1000 live births [1], the lowest rate (1.4 children per 1000 live births/neonatal survivors) being observed in Australia [3]. Our data provide valuable insights on the high burden and severity of CP in a hospital-based cohort in Vietnam. This is possibly reflecting the greater burden of perinatal risk factors (e.g., asphyxia, infections, prematurity) and poor access to perinatal care and rehabilitation commonly observed in LMICs [5,14–18].

The complete causal pathway of the brain injury causing CP is poorly understood. CP is associated with numerous prenatal and perinatal factors, such as perinatal asphyxia, neonatal jaundice, infections, preterm birth, low birth weight, multiple pregnancy and birth defects [18]. We reported the proportions of our cohort

with these prenatal and perinatal factors in Table 3. Identification of known aetiologies of CP can be challenging in low resource settings in absence of the tools available in HICs [17]. The presumed timing of the brain injury causing CP was unknown for 31.7% of our cohort. Studies have defined prenatal, perinatal and postnatal causes variably and cases that have not been identified to have any known postnatal cause are often believed to have resulted from brain injury during the prenatal or perinatal period [17].

Findings from similar settings can also vary due to methodological differences. In our hospital-based cohort, majority of the mothers received regular antenatal care (86.5%, n = 652) and had institutional delivery of their child in a hospital (90.8%, n = 687). These findings markedly differ from the community-based studies conducted in Bangladesh and Indonesia where considerably fewer mothers received regular antenatal care (Bangladesh: 30.3%, Indonesia: 55.4%) and the majority (Bangladesh: 72.7%, Indonesia: 72.3%) of the children were delivered at home [5,16].

We have identified modifiable risk factors for CP and poor outcomes in many children, including hyperbilirubinemia, poor nutrition, lack of mobility devices and limited access to multidisciplinary services. This suggests opportunities for prevention of CP and its co-morbidities, decreasing disease severity, and improving quality of life for children with CP in Vietnam. In addition, we describe the clinical type, severity, associated impairments and rehabilitation status of children with CP. This information will inform clinician education and training, health policy and service planning and identify opportunities for evidence-based diagnosis and therapy.

Although evidence-based diagnosis and management approaches to CP have proven effective in HICs [19], there is limited information about their use in Vietnam. There are practical limitations to the use of some assessment methods and treatments. For example, the lack of dietitians precludes adequate nutritional assessment and treatment and, interventions, such as continuous nasogastric feeding, are not readily available [20]. Similarly, access to mobility aids is limited in Vietnam. Only 12 of the 454 children from our cohort with GMFCS III to V had access to assistive devices e.g. wheelchairs. The lack of availability of allied health professionals in Vietnam, including speech and occupational therapists, is a major limitation to optimal, multidisciplinary management of children with CP and diverse needs. Integration of these evidence-based approaches into current practice would improve management of children with CP in Vietnam substantially. Clinical guidelines for the management of children with CP have been developed and approved by the Vietnamese Ministry of Health and their implementation is currently underway across Vietnam [21].

Early intervention is limited by delayed diagnosis in LMICs, which contributes to poor motor and cognitive outcomes, is associated with secondary complications including contractures and malnutrition and negatively impacts carer wellbeing [22]. The mean age of diagnosis of CP was 1.7 years in our cohort. Owing to the hospital-based recruitment of our cohort we are unaware of the timing of CP diagnosis for majority of the community cases. It is likely to be delayed due to a range of reasons which are commonly observed in LMICs, such as poverty, poor educational status, lack of awareness and limited access to health information [5,23]. Community-based studies from other LMICs have documented delayed diagnosis at 5.2 years and 6.4 years in Bangladesh and Indonesia respectively [5,16]. In contrast, HICs such as Australia reported a mean age of CP diagnosis at 1.4 years [22]. Use of evidence-based approaches including the General

Table 3. Characteristics of pregnancy and perinatal period.

	n (%)
Mothers with previous stillbirths more than 20 weeks (n = 729)	31 (4.3)
Mothers with previous miscarriages less than 20 weeks (n = 747)	125 (16.7)
Family member with a disability (n = 748)	76 (10.2)
Sibling	29 (3.9)
One or both parents	18 (2.4)
Cerebral palsy	21 (2.8)
Agent Orange poisoning	3 (0.4)
Parent consanguinity (n = 744)	11 (1.5)
Assisted conception (n = 736)	13 (1.8)
In vitro fertilisation (IVF)	7 (1.0)
Ovulation stimulation only	3 (0.4)
Artificial insemination	2 (0.3)
Gamete intrafallopian transfer (GIFT)	1 (0.1)
Antenatal care (n = 754)	
No	31 (4.1)
Regular	652 (86.5)
Irregular (>2 visits)	60 (8.0)
Irregular (≤2 visits)	11 (1.5)
Maternal febrile illness during pregnancy (n = 762)	102 (13.4)
Maternal febrile rash (n = 680)	18 (2.6)
Maternal febrile illness during labour (n = 752)	16 (2.1)
Place of birth (n = 757)	
Hospital	687 (90.8)
Health care centre	60 (7.9)
Home	10 (1.3)
Mode of delivery (n = 756)	
Vaginal birth	504 (66.7)
Caesarean section	238 (31.5)
Instrumental delivery (forceps or ventouse suction)	14 (1.9)
Maternal complications during childbirth (n = 736)	170 (23.1)
Mean gestational age and range (n = 762)	37.2 ± 4.5; 25–43
Term (≥37–41 weeks)	541 (71.0)
Preterm (≤36 weeks)	202 (26.5)
Most preterm (≤27 weeks)	11 (5.4)
Very preterm (28–31 weeks)	64 (31.7)
Moderate preterm (32–33 weeks)	46 (22.8)
Late preterm (34–36 weeks)	81 (40.1)
Post-term (42 − 43 weeks)	19 (2.5)
Mean birthweight and SD (grams)	2783 ± 708.0
Low birthweight (<2500 g)	200 (26.3)
Multiple birth (n = 733)[a]	31 (4.2)
Early feeding difficulties (n = 742)	168 (22.6)
Birth defects[b]	112 (14.8)
Brain anomalies	5 (4.5)
Known syndromes (n = 726)	67 (9.2)
Perinatal asphyxia (n = 761)	276 (36.3)
Neonatal jaundice	81 (10.7)
Infection	69 (9.1)
Brain haemorrhage	28 (3.7)
Traumatic/accidental brain injury	11 (1.4)
Hospital neonatal transfer (n = 538)	460 (85.5)
Central/national	128 (27.8)
District	106 (23.0))
Provincial	226 (49.1)
Mean length of stay at hospital of neonatal transfer (days) and range	18.7 ± 16.2; 1–114
Type of care received at hospital of neonatal transfer (n = 696)	
NICU	242 (31.6)
Special care	43 (5.6)
Routine care only	411 (53.7)
Mean number of hospitalisations for chest infections/ respiratory infections in the last 6 months and range (n = 745)	0.4 ± 1.0; 1–10

[a]one triplet and 30 twin pregnancies.
[b]a birth defect is defined as a structural anomaly present at birth, involving the face, limbs or any organ system. The presence of birth defects was determined by a paediatrician based on clinical assessment, review of hospital records, relevant investigations and parent report.

Table 4. Immunisation, education and rehabilitation status.

	n (%)
Fully vaccinated (n = 753)	623 (82.7)
BCG (n = 746)	701 (94.0)
MR (n = 512)	373 (72.9)
Reason for no vaccination (n = 80)	
Child was ill	64 (80.0)
No access at local centre or no transport to travel	3 (3.8)
Convulsions/post injection seizures	5 (6.3)
Family refused	2 (2.5)
Forgot immunization date	1 (1.3)
Unknown	5 (6.3)
Attend mainstream school (n = 75)[a]	
No	23 (30.7)
Yes	52 (69.3)
Primary	46 (88.4)
Secondary	5 (9.6)
Vocational/other	1 (1.9)
Attend special school (n = 725)	9 (1.2)
Received rehabilitation (n = 703)[b]	
Therapy exercises	663 (94.3)
Advice	151 (21.5)
Assistive device[c]	81 (11.5)
Muscle relaxant	5 (0.7)
Surgery	5 (0.7)
Acupuncture	1 (0.1)
Age of first rehab and range (years) (n = 694)	1.1 ± 1; 0–13
Location of rehabilitation service (n = 659)[d]	
Home	585 (88.8)
Hospital	334 (50.7)
Private clinic	4 (0.6)

[a]School attendance is applicable for 75 children aged ≥6 years.
[b]Many participants received more than one type of rehabilitation.
[c]Assistive devices included wheelchairs and walkers.
[d]Many participants received treatment at more than one location.

Movements Assessment, Hammersmith Infant Neurological Examination and MRI in HICs make the diagnosis of CP possible with high predictive value as early as 5 months of age [22]. Even with the use of these approaches, however early diagnosis of CP can be challenging in HICs, particularly in milder cases and children with multiple associated impairments.

It was previously believed that improved neonatal care may increase survival rates and adverse neurodevelopmental outcomes including CP and poor quality of life. However, recent findings from Australia and Europe show that following an initial spike in the rate of CP among survivors, in recent years optimal NICU care is associated with decreasing rates of CP [24]. HICs have observed reductions in both the burden and severity of CP over recent decades with advances in evidence-based healthcare practices and public health initiatives [2,21]. Findings from our study can potentially guide the warranted strategies in Vietnam to achieve the successes observed in HICs in addressing the burden of CP.

In HICs the administration of magnesium sulphate to mothers at risk of a preterm birth has proven effective and holds tremendous potential in LMICs [25]. Preterm births, a leading risk factors for CP in HICs, are underrepresented in our cohort (Vietnam: 26.5%, Australia: 43.0%) [3]. This is possibly due to the high mortality among preterm babies born in LMICs and the failure to prevent, identify and treat preventable risk factors such as infection, asphyxia and hyperbillirubinemia [5,19]. However, the rate of preterm births among our cohort is significantly higher than the proportion of 9.0% among the general population of Vietnam [26]. Furthermore, children with CP are at high risk of incomplete and delayed immunisation compared to the general population which is consistent with our findings [27].

Although Vietnam has seen improved nutrition and child and maternal survival rates, health disparity across sociodemographic gradients is significant [28]. Over two thirds (68.8%) of our cohort were living below the national poverty line, which is substantially higher than the 20.7% among the general population [8].

Socioeconomic deprivation is often both a cause and consequence of having a child with CP [29]. Low socioeconomic status is associated with increased risk of CP and contributes to more severe functional limitations owing to greater exposure to risk factors and limited access to healthcare [30,31]. High parental unemployment rates (maternal: 35.0% and paternal: 24.5%) were observed in our cohort [32]. This is substantially higher than the national unemployment rate of 3.2%. Larger than average household size is known to be associated with poverty and we observed a household size of 4.7 members per household in our cohort compared to the national average of 3.5 members per household [33,34]. The Kinh ethnic group accounts for 85.3% of the total population in Vietnam and 97.9% of the total population of the Red River Delta region where our study site is located; we speculate that the burden and severity of CP would be even greater than in our cohort among ethnic minority groups and children living in remote or disadvantaged provinces in Vietnam who are more vulnerable to the known risk factors associated with CP [35].

Limitations

Although this study has yielded valuable new insights into the epidemiology of CP in Vietnam, the cohort is not population representative, thus we were unable to document prevalence. Furthermore, we do not know how generalisable these findings are to other provinces. Hospital-based recruitment, disparity in access to health care, and variable health-seeking behaviour may have resulted in selection bias. For example, there may have been underreporting of milder cases, children from poorer or less educated families and children from rural or remote settings. Similarly, a high proportion of our cohort had quadriplegia which may reflect overreporting of severe cases. In LMICs, premature mortality is high among children with CP and occurs well before the average age of CP diagnosis in LMICs [36]. Our surveillance does not capture children who died prior to diagnosis. Despite these limitations these data were collected using a well-established method, from the main paediatric referral hospital (NCH) in the most densely populated region of Vietnam (the Red River Delta Region) and serves the majority of that child population.

Although cognitive delay may be evident in young children, it may be transient. Intellectual impairment cannot be formally confirmed until ~5 years of age, when standardised, valid measures that are predictive and reliable can be used [37]. In our study, assessment of intellectual impairment or cognitive delay was based on clinical assessment, report by the parents/primary caregivers or review of existing medical records, as most of our cohort is under 5 years of age. We acknowledge that a limitation of the study is the inability to accurately estimate the proportion who will have ongoing intellectual impairment.

We were unable to conduct detailed assessment of the associated impairments due to limited access to audiology, formal testing of speech and language and cognitive testing. We relied on clinical history, detailed assessment conducted by clinicians and report by the parents/primary caregivers. History taking from parents by the clinicians on retrospective data is subject to recall bias.

Despite its limitations, this study provides baseline descriptive data on a large cohort of children with CP in Vietnam. Although there is likely selection bias, our findings demonstrate a high burden of CP on the hospital system and in the absence of any such data on children with CP in Vietnam we believe our study findings are valuable in identifying opportunities for prevention,

needs for diagnostic tools, therapy and equipment, and service planning and training needs.

Conclusion

We established a hospital-based, prospective surveillance system to identify and describe children with CP. Our novel data reveal a high burden and severity of CP in this hospital setting and opportunities for prevention. Our data will inform clinician education and training, health policy, service planning and evidence-based diagnosis and therapy.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Nutritional Status of Children with Cerebral Palsy—Findings from Prospective Hospital-Based Surveillance in Vietnam Indicate a Need for Action

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Abstract: Background: Lack of evidence on the burden and risk factors for malnutrition among children with cerebral palsy (CP) in Vietnam limits evidence-based interventions. We aimed to define the nutritional status of children with CP in Vietnam. Materials and Methods: The study utilized data from active prospective hospital-based surveillance modelled on the Pediatric Active Enhanced Disease Surveillance system. Children (0–18 years) with CP attending the National Children's Hospital Hanoi, Vietnam between June–November 2017 were included. Data on demographic, clinical and rehabilitation status were collected following detailed neurodevelopmental assessment. Anthropometric measurements were taken. Nutritional status was determined using the World Health Organization guideline. Results: Of 765 children (the mean (SD) age was 2.6 (2.5) years; 35.8% were female), 28.9% (n = 213) were underweight and 29.0% (n = 214) stunted. The odds of underweight were significantly higher among children aged >5 years and/or having a monthly family income of <50 USD. Underweight and/or stunting was high among children with quadriplegia (81%, n = 60 and 84.5%, n = 87) and/or Gross Motor Functional Classification System (GMFCS) level IV–V (62.5%, n = 45 and 67.0%, n = 67). Nearly one-third of intellectually impaired and more than half of hearing-impaired children were underweight and/or stunted. Conclusions: Poor economic status and increased motor severity increased vulnerability to malnutrition. Our findings will inform nutritional rehabilitation programs among these vulnerable children.

Keywords: cerebral palsy; hospital-based surveillance; malnutrition; Vietnam; children

1. Introduction

Poor nutrition and growth faltering disrupt cognition and development and are commonly observed among children with Cerebral Palsy (CP). CP is a major cause of childhood disability. It is a non-progressive neurological disorder resulting from an insult to the developing brain that affects posture and movement [1]. Oromotor dysfunction and gastrointestinal problems, often associated with motor impairment, hinder optimum nutrition of children with CP [2,3]. The worldwide prevalence of CP is 2.1 per 1000 live births with a rate of 1.4 per 1000 live births observed in Australia [4,5]. However, a recent population-based study in Bangladesh reported a prevalence of 3.4 per 1000 live births [6]. This is substantially higher than the global estimate, which largely reflects findings from high income countries (HICs). This disparity is most likely due to increased risk factors, including birthing practices, in a poor socio-economic context [7,8], which is also a key underlying risk factor for malnutrition among children [9].

Maintenance of optimal nutrition is challenging among children with CP. Although, studies from both HICs and low and middle-income countries (LMICs) have demonstrated high prevalence of malnutrition among children with CP compared to the general population [10,11], evidence suggests that the burden is considerably higher in LMICs than in HICs [10–12]. Yet the underlying risk factors in LMICs are poorly understood. Severe motor impairment, measured using the Gross Motor Functional Classification System (GMFCS), presence of associated impairments and oropharyngeal dysphagia affect the nutritional status of children with CP [2,10,12].

Feeding difficulties among children with CP increase their risk of growth failure [3]. A population-based study in Norway reported significantly higher longitudinal growth faltering in the first five years of age among children with CP who had feeding difficulties compared to their peers without such difficulties [11]. In Ghana, children with CP and feeding difficulties had 3 to 10 times higher odds of being underweight than children with CP without feeding difficulties [13]. Similar patterns were observed in Uganda [14]. Moreover, children with CP are at high risk of poor nutritional outcome due to metabolic alterations and changes in body composition for example, decreased fat free mass, changes in body fat level and altered calorie demand, associated with CP [15]. In LMICs, the significance of these risk factors is likely to be intensified due to their complex interaction with socio-economic factors.

Adverse consequences of malnutrition among children with CP are widespread. Evidence from different countries reveals that malnutrition among children with CP results in poor health-related outcomes, poor quality of life and premature mortality [16,17]. The vicious cycle of malnutrition and infection has also been illustrated in several studies [18]. In a recent population-based study in Bangladesh, 86% of deaths among children with CP were attributed to infections and nearly all of the children who died were undernourished [16]. Studies conducted in Bangladesh and Ghana also reported poor quality of life among the caregivers of children with CP and feeding difficulties [13,19]. Existing evidence suggests that the scenario is likely to be similar for children with CP in the resource constraint settings of other LMICs such as Vietnam.

Nutritional interventions such as gastrostomy and tube feeding are beneficial for weight gain among children with CP [20]. However, such interventions are not commonly available or used in low resource settings and are reportedly poorly understood by clinicians and families. Furthermore, in LMICs there is limited access to dieticians and speech pathologists, who play a crucial role in the management of feeding problems among children with CP. Better understanding of the nutritional status of children with CP is essential to guide the development of evidence-based programs suitable for these settings. In this study we aimed to assess the burden of malnutrition and the underlying risk factors among children with CP in Vietnam.

2. Materials and Methods

The study utilized data from an active hospital-based surveillance of children with CP in the National Children's Hospital in Hanoi, Vietnam [21]. The diagnosis of CP was made using the standard definition adopted from Surveillance of Cerebral Palsy in Europe and the Australian CP Register [5,22].

2.1. Study Setting and Participants

Study participants included children aged ≤18 years who visited the National Children's Hospital in Hanoi, Vietnam between June and November 2017 and were diagnosed with CP.

2.2. Data Collection and Clinical Assessment

Data were recorded by trained clinicians using a standardized case record form in the Vietnamese language and responses were translated into English by two clinicians on the study team. Sociodemographic factors (e.g., age, gender, income, educational level of the parents), clinical factors (e.g., GMFCS level, Manual Ability Classification System (MACS) level, predominant CP motor type, associated impairments) and anthropometric measurements (e.g., weight, height) were collected as part of the registration and clinical assessment process. A detailed study protocol including the methods and measures used in the study has been published previously [21].

2.3. Anthropometric Measurements

We measured height and weight using a standard World Health Organization (WHO) guideline [23].

Weight: Weight was measured in kilograms using a digital weighing scale with a precision of 100 g following standard guidelines (i.e., removing extra clothing, standing still). Tared weight was measured for young children aged less than 2 years and for children who could not stand alone. Clinicians were trained before taking anthropometric measurements. Three repeated measures were taken and the average was noted in the questionnaire.

Height: Recumbent length was measured in cm for children aged less than 2 years using a length board and standing height was measured for children aged ≥2 years using a standing frame. The mean of three repeated measures were taken to minimize measurement error. For children who could not stand alone, segmental height (i.e., knee height) was measured and full height was derived using the following formula; height = (2.69 × knee height) + 24.2 cm [24].

2.4. Data Management and Analysis

Data entry and analyses were carried out using SPSS version 23.0 (IBM Corporation, Chicago, IL, USA). All data were entered into a database by investigators in Sydney and Vietnam. Three indices were used to describe the nutritional status of children with CP—weight for age (WA), height for age (HA) and weight for height (WH). The z scores for these three indices (i.e., WAZ, HAZ and WHZ) were calculated using WHO Anthro (version 3.2) and WHO AnthroPlus software. WAZ was calculated for children aged less than 121 months and WHZ was calculated for children aged less than 61 months. Nutritional status of children was categorized using the WHO cutoffs for the z scores (i.e., −2SD to +2SD: Normal; <−2SD to −3SD: Moderately undernourished and <−3SD: Severely undernourished).

A normality test was conducted for all continuous variables for example, WAZ, HAZ and WHZ using Shapiro Wilk test. In case of variables not normally distributed [WAZ, HAZ, WHZ] we used median [IQR]). Descriptive analyses were done to present socio-demographic characteristics, clinical factors and nutritional status of the study participants. Bivariate analyses were done to identify potential risk factors for malnutrition among children with CP. Chi-square and Fisher's exact tests were used to examine the statistical differences in nutritional status between groups of children according to their socio-demographic characteristics and clinical factors. The nutritional status of children with CP aged less than five years was compared with the general population of the same age group in Vietnam using World Bank data. Binomial test were done to identify statistically significant differences between the proportion of malnutrition among our study participants and a general population of the same age group. Factors that were found to be related to underweight and/or stunting among children in bivariate analyses for example, chi-square test, Fisher's exact tests and unadjusted logistic

regression were included in an adjusted logistics regression model. A *p* value < 0.05 was considered statistically significant.

2.5. Ethical Consideration

Ethics approval was obtained from the University of Sydney Human Research Ethics Committee (HREC) (2016/456), Hanoi Medical University (HMU) (1722/QD-QHYHN) and NCH (812/QD-BVNTU) in Hanoi, Vietnam. Informed consent was obtained from parents or caregivers of all the study participants.

3. Results

A total of 765 children with CP and aged less than 18 years was identified between June and November 2017. The mean (SD) age was 2.6 (2.5) years and 35.8% were female.

3.1. Overall Nutritional Status

Of the 765 children 71.1% (n = 524) had a normal WAZ, 70.1% (n = 502) had a normal HAZ and 75.1% (n = 435) children had a normal WHZ. The distribution of WAZ, HAZ and WHZ was positively skewed, hence the median [IQR] for these three indicators was reported. The median [IQR] z score for WAZ was −1.3 [−2.2, −0.2], the median z score for HAZ was −1.1 [−2.3, 0.2] and the median z score for WHZ was −0.86 [−2.0, 0.3]. Among the children, 28.9% (n = 213) were underweight, 29.9% (n = 214) were stunted and 24.9% (n = 144) were wasted. When compared to children aged under five years in the general population in Vietnam, children aged less than five years with CP had a significantly higher prevalence of underweight, stunting and wasting (*p* < 0.001 for all three indices). Moreover, 14.4% (n = 103) of children with CP had severe chronic malnutrition (i.e., severe stunting) and 13.8% (n = 80) had severe acute malnutrition (SAM) (i.e., severe wasting). (Table 1)

Table 1. Nutritional status of the study participants.

Indicators	Children with CP in Our Study			General Population (Aged <5 Years) in 2015 [1]	*p* Value [2]
	Overall		Aged <5 Years		
	Median [IQR]	n (%)	n (%)	(%)	
Weight-for-age z score (*n* = 737) [3]					
Normal		524 (71.1)	–	–	
Underweight	−1.25 [−2.2, −0.2]				**<0.001**
Moderate		139 (18.9)	176 (27.7)	14.1	
Severe		74 (10.0)			
Height-for-age z score (*n* = 716) [4]					
Normal		502 (70.1)	–	–	
Stunted	−1.1 [−2.3, 0.2]				**<0.001**
Moderate		111 (15.5)	184 (30.6)	24.6	
Severe		103 (14.4)			
Weight-for-height z score (*n* = 579) [5]					
Normal		435 (75.1)	–	–	
Wasted	−0.86 [−2.0, 0.3]				**<0.001**
Moderate		64 (11.1)	142 (24.7)	6.4	
Severe		80 (13.8)			

[1] The World Bank data, 2015. Available from: https://data.worldbank.org. [2] Binomial test. [3] Weight-for-age z score was calculated for children aged ≤121 months. [4] Missing data (n = 49). [5] Weight-for-height z score was calculated for children aged ≤61 months. The *p* values for statistically significant differences are shown in bold.

3.2. Socio-Demographic Characteristics and Nutritional Status of Children with CP

Table 2 summarizes the nutritional status of study participants according to their socio-demographic characteristics. A significant inverse relationship was observed between age group

and proportion of underweight among children with CP. Among children aged less than two years, 25.3% (*n* = 106) were underweight. The proportion of underweight was significantly higher among children aged 2–4 years (32.3%, *n* = 70) and ≥5 years (36.6%, *n* = 37) (*p* = 0.03). Conversely, stunting was less prevalent among children aged ≥5 years.

Table 2. Socio-demographic characteristics of children and their nutritional status.

Indicators	Total	Weight-for-Age Z Score (*n* = 737) [1]			Height-for-Age Z Score (*n* = 716) [2]		
	n = 765	Normal *n* = 524	Underweight *n* = 213	*p* Value [3]	Normal *n* = 502	Stunted *n* = 214	*p* Value [3]
Age groups (years), *n* **= 765**							
less than 2	424 (55.4)	313 (74.7)	106 (25.3)	**0.03**	282 (72.3)	108 (27.7)	0.07
2–4	220 (28.8)	147 (67.7)	70 (32.3)		135 (64.0)	76 (36.0)	
5 and more	121 (15.8)	64 (63.4)	37 (36.6)		85 (73.9)	30 (26.1)	
Sex, *n* **= 765**							
Female	274 (35.8)	200 (75.2)	66 (24.8)	0.07	184 (71.6)	73 (24.8)	0.52
Male	491 (64.2)	324 (68.8)	147 (31.2)		318 (69.3)	141 (30.7)	
Source of drinking water, *n* **= 761**							
Piped water	423 (55.6)	308 (75.3)	101 (24.7)	**0.01**	287 (72.8)	107 (27.2)	0.17
Well water	284 (37.3)	182 (66.9)	90 (33.1)		179 (66.8)	89 (33.2)	
Other sources (ponds/river/stream/lake)	54 (7.1)	31 (58.5)	22 (41.5)		33 (64.7)	18 (35.3)	
Sanitation practice, *n* **= 759**							
Flush toilet	633 (83.4)	439 (72.1)	170 (27.9)	0.18	425 (71.7)	168 (28.3)	**0.04**
Pit toilet	126 (16.6)	82 (66.1)	42 (33.9)		74 (62.2)	45 (37.8)	
Monthly family income, *n* **= 728**							
below 50 USD	180 (24.7)	104 (60.5)	68 (39.5)	**0.002**	110 (65.1)	59 (34.9)	0.23
51-100 USD	231 (31.7)	158 (71.8)	62 (28.2)		154 (70.0)	66 (30.0)	
101-150 USD	153 (21.0)	109 (73.6)	39 (26.4)		103 (71.5)	41 (28.5)	
Above 150 USD	164 (22.5)	127 (78.9)	34 (21.1)		112 (75.7)	36 (24.3)	

[1] Weight-for-age z score was calculated for children aged ≤121 months. [2] Missing data (n = 49). [3] Chi square test. The *p* values for statistically significant differences are shown in bold.

The burden of underweight was significantly higher among children who did not have access to safe drinking water compared to those who had access (24.7%, *n* = 101 vs. 41.5%, *n* = 22; *p* = 0.01). Although not statistically significant, a similar finding was observed for stunting among children with CP in our cohort.

Rates of both underweight (39.5%, *n* = 68) and stunting (34.9%, *n* = 59) were highest among children whose monthly family income was less than 50 USD. When compared with the proportion of underweight children in families in our cohort with a monthly family income of >150 USD (21.1%, *n* = 34) the difference was significant (*p* < 0.001). Although stunting was more prevalent among children with a monthly family income of <50 USD compared to those with higher income, this difference was not statistically significant (*p* = 0.23).

3.3. Clinical Characteristics and Nutritional Status of Children With CP

3.3.1. Age of CP Diagnosis and Timing of CP

Although not statistically significant, both underweight and stunting were slightly higher among children who had a confirmed diagnosis of CP at or over five years of age than others in the cohort. Similarly, children with pre and perinatally acquired CP had higher rates of underweight and stunting than children with postnatally acquired CP. (Table 3)

Table 3. Clinical characteristics and nutritional status of the children with Cerebral Palsy (CP).

Indicators	Total	Weight-for-Age Z Score, (n = 737) [1]			Height-for-Age Z Score, (n = 716) [2]		
	n = 765	Normal n = 524 n (%)	Underweight n = 213 n (%)	p Value [3]	Normal n = 502 n (%)	Stunted n = 214 n (%)	p Value [3]
Age of CP diagnosis (years), n = 754							
less than 2	559 (74.1)	395 (72.2)	152 (27.8)		370 (70.7)	153 (29.3)	
2–4	143 (19.0)	95 (68.3)	44 (31.7)	0.45	94 (68.6)	43 (31.4)	0.87
5 and more	52 (6.9)	28 (65.1)	15 (34.9)		33 (68.8)	15 (31.3)	
Timing of CP, n = 753							
Postnatal	98 (13.0)	72 (75.0)	24 (25.0)		72 (76.6)	22 (23.4)	
Pre and perinatal	416 (55.2)	279 (69.4)	123 (30.6)	0.44	259 (66.4)	131 (33.6)	0.05
Unknown	239 (31.7)	167 (72.9)	62 (27.1)		165 (74.0)	58 (26.0)	
GMFCS level, n = 754							
I	179 (23.7)	125 (76.7)	38 (23.3)		134 (78.8)	36 (21.2)	
II	121 (16.0)	89 (76.7)	27 (23.3)		80 (69.6)	35 (30.4)	
III	103 (13.7)	76 (73.8)	27 (26.2)	**0.04**	71 (75.5)	23 (24.5)	**0.01**
IV	131 (17.4)	88 (68.8)	40 (31.3)		81 (65.9)	42 (34.1)	
V	220 (29.2)	140 (64.2)	78 (35.8)		129 (63.2)	75 (36.8)	
MACS level, n = 188							
I	71 (37.8)	44 (72.1)	17 (27.9)		48 (70.6)	20 (29.4)	
II	73 (38.8)	47 (69.1)	21 (30.9)		48 (69.6)	21 (30.4)	
III	26 (13.8)	17 (70.8)	7 (29.2)	0.77	18 (75.0)	6 (25.0)	0.58 [4]
IV	17 (9.0)	10 (58.8)	7 (41.1)		11 (64.7)	6 (35.3)	
V	1 (0.5)	-	-		0 (0.0)	1 (100.0)	
Neurological type of CP, n = 765							
Mono/hemi	157 (20.5)	118 (79.2)	31 (20.8)		119 (79.9)	30 (20.1)	
Diplegia	40 (5.2)	30 (76.9)	9 (23.1)		29 (76.3)	9 (23.7)	
Triplegia	0 (0.0)	0 (0.0)	0 (0.0)	0.10 [4]	0 (0.0)	0 (0.0)	**0.01** [4]
Quadriplegia	532 (69.5)	352 (68.2)	164 (31.8)		328 (66.4)	166 (33.6)	
Ataxia	1 (0.1)	1 (100.0)	0 (0.0)		0 (0.0)	1 (100.0)	
Dyskinesia	35 (4.6)	23 (71.9)	9 (28.1)		26 (76.5)	8 (23.5)	
Number of associated impairments, n = 765							

Table 3. *Cont.*

Indicators	Total	Weight-for-Age Z Score, (*n* = 737) [1]			Height-for-Age Z Score, (*n* = 716) [2]		
	n = 765	Normal *n* = 524 n (%)	Underweight *n* = 213 n (%)	*p* Value [3]	Normal *n* = 502 n (%)	Stunted *n* = 214 n (%)	*p* Value [3]
None	196 (25.6)	143 (78.1)	40 (21.9)		146 (78.5)	40 (21.5)	
At least one	206 (26.9)	145 (72.1)	56 (27.9)	**0.02**	131 (70.1)	56 (29.9)	**0.01**
Multiple	363 (47.5)	236 (66.9)	117 (33.1)		225 (65.6)	118 (34.4)	
Type of associated impairments							
Epilepsy	82 (10.8)	54 (68.4)	25 (31.6)	0.41	56 (71.8)	22 (28.2)	0.71
Intellectual	439 (65.6)	283 (66.6)	142 (33.4)	**0.001**	273 (65.5)	144 (34.5)	**<0.001**
Visual	40 (5.4)	24 (61.5)	15 (38.5)	0.11	21 (53.8)	18 (46.2)	**0.02**
Hearing	13 (1.7)	6 (46.2)	7 (53.8)	**0.04**	9 (69.2)	4 (30.8)	0.60 [4]
Speech	449 (63.7)	305 (69.2)	136 (30.8)	0.07	281 (67.9)	133 (32.1)	**0.04**
Swallowing difficulties, *n* = 740							
Present	60 (8.1)	39 (7.7)	20 (9.6)	0.39	38 (7.8)	18 (8.8)	0.64
Absent	680 (91.9)	469 (92.3)	188 (90.4)		451 (92.2)	186 (91.2)	
Received rehabilitation services, *n* = 759							
Ever received rehabilitation services	703 (92.6)	483 (70.9)	198 (29.1)	0.56	461 (69.1)	206 (30.9)	**0.03**

[1] Weight-for-age z score was calculated for children aged ≤121 months. [2] Missing data (*n* = 49). [3] Chi square test. [4] Fisher's exact test. The *p* values for statistically significant differences are shown in bold.

3.3.2. Motor Severity and Neurological Type of CP

The proportion of children with underweight was significantly higher among those with GMFCS level V than in children with GMFCS level I (35.8%, *n* = 78 vs. 23.3%, *n* = 38; *p* = 0.04), as was the proportion with stunting (36.8%, *n* = 75 vs. 21.2%, *n* = 36; *p* = 0.01). A similar pattern was observed for MACS level among children aged 4 years and above. Among children with MACS level IV, 41.1% (*n* = 7) were underweight and 35.5% (*n* = 6) were stunted, whereas these percentages were 27.9% (*n* = 17) and 29.4% (*n* = 20) respectively for children with MACS level I (*p* = 0.77 and *p* = 0.58 respectively).

The majority of children in our study had spastic CP, however none had triplegia. Both underweight (31.8%, *n* = 164) and stunting (33.6%, *n* = 166) were more commonly observed among children with quadriplegia than the children without quadriplegia (*p* = 0.01). (Table 3)

3.3.3. Associated Impairments

In our study, 74.4% (*n* = 569) children had one or multiple associated impairments. Among the children who had one or more associated impairments, 33.1% (*n* = 117) were underweight and 34.4% (*n* = 118) were stunted. The proportion with underweight or stunting was significantly higher among children with one or multiple associated impairments (*p* = 0.02 and *p* = 0.01 respectively) than with no associated impairments. Both underweight and stunting were significantly higher among children reported to have intellectual impairment (*p* < 0.001) or hearing impairment (*p* < 0.001) compared to children without these impairments. (Table 3)

3.3.4. Factors Associated with Underweight and Stunting among Children with CP

Tables 4 and 5 present findings from unadjusted and adjusted analyses. In the adjusted analysis, the odds of being underweight was statistically associated with the age of the children, monthly family income and GMFCS level. Children aged more than five years had 3.2 times higher odds of being underweight than children aged less than two years. When adjusted for other covariates, children from the poorest families (monthly family income <50 USD) had 3.0 times higher odds of being underweight than children whose monthly family income was >150 USD.

Monthly family income was not significantly associated with stunting. However, children between 2 and 4 years of age had higher odds of being stunted than younger children. When adjusted for covariates, the presence of intellectual impairment and motor function at GMFCS levels IV and V significantly increased the odds of stunting. Similarly, underweight was associated with GMFCS levels IV and V but there was no association between intellectual impairment and the level of underweight.

Table 4. Factors associated with underweight and stunting among children with CP in Vietnam (unadjusted analyses).

Covariates	Underweight		Stunting	
	Odds Ratio (95% CI) (Unadjusted)	*p* Value	Odds Ratio (95% CI) (Unadjusted)	*p* Value
Age group (years)				
less than 2	Reference			
2–4	1.4 (1.0, 2.0)	0.63	1.5 (1.2, 2.1)	**0.03**
5 and more	1.7 (1.1, 2.7)	**0.02**	0.9 (0.6, 1.5)	0.73
Source of drinking water				
Well water	Reference			
Piped water	0.7 (0.5, 0.9)	**0.02**	0.7 (0.5, 1.0)	0.09
Other sources (ponds/river/stream/lake)	1.4 (0.8, 2.6)	0.24	1.1 (0.6, 2.5)	0.77

Table 4. *Cont.*

Covariates	Underweight		Stunting	
	Odds Ratio (95% CI) (Unadjusted)	*p* Value	Odds Ratio (95% CI) (Unadjusted)	*p* Value
Monthly family income (USD)				
Above 150	*Reference*			
below 50	2.4 (1.5, 4.0)	**<0.001**	1.7 (1.0, 2.7)	0.04
51–100	1.5 (0.9, 2.4)	0.12	1.3 (0.8, 2.1)	0.23
101–150	1.3 (0.8, 2.3)	0.28	1.2 (0.7, 2.1)	0.42
GMFCS level				
I	*Reference*			
II	1.0 (0.6, 1.7)	0.99	1.6 (0.9, 2.8)	0.08
III	1.2 (0.7, 2.1)	0.59	1.2 (0.7, 2.2)	0.54
IV	1.5 (0.9, 2.5)	0.13	1.9 (1.1, 3.2)	**0.01**
V	1.8 (1.2, 2.9)	**0.01**	2.2 (1.3, 3.4)	**0.001**
Intellectual impairment				
No	*Reference*			
Yes	0.5 (0.4, 0.8)	**0.001**	0.5 (0.3, 0.7)	**<0.001**
Hearing impairment				
No	*Reference*			
Yes	0.3 (0.1, 1.0)	0.05	0.9 (0.3, 3.1)	0.93
Visual impairment				
No	*Reference*			
Yes	0.6 (0.3, 1.2)	0.17	0.5 (0.2, 0.9)	**0.02**
Speech Impairment				
No	*Reference*			
Yes	0.7 (0.5, 1.1)	0.12	0.7 (0.5, 1.0)	0.04
Neurological type of CP [1]				
Mono/hemiplegia	*Reference*			
Diplegia	1.1 (0.5, 2.6)	0.76	1.2 (0.5, 2.9)	0.63
Quadriplegia	1.8 (1.1, 2.7)	0.01	2.0 (1.3, 3.1)	0.002
Dyskinesia	1.5 (0.6, 3.5)	0.37	1.2 (0.5, 3.0)	0.66

[1] There were no triplegic child and one Ataxic child in our cohort. Due to the smaller size, we have excluded these two categories from this unadjusted analysis. The *p* values for statistically significant differences are shown in bold.

Table 5. Factors associated with underweight and stunting among children with CP in Vietnam (unadjusted analysis).

Covariates	Underweight		Stunting	
	Odds Ratio (95% CI) (Adjusted)	*p* Value	Odds Ratio (95% CI) (Adjusted)	*p* Value
Age group (years)				
less than 2	*Reference*			
2–4	2.1 (1.3, 3.5)	**0.002**	2.0 (1.3, 3.2)	**0.003**
5 and more	3.1 (1.7, 6.1)	**0.001**	1.2 (0.6, 2.4)	0.58
Source of drinking water				
Well water	*Reference*			
Piped water	0.9 (0.5, 1.3)	0.52	0.8 (0.5, 1.3)	0.47
Other sources (ponds/river/stream/lake)	1.4 (0.7, 2.9)	0.38	1.2 (0.5, 2.5)	0.65

Table 5. *Cont.*

Covariates	Underweight		Stunting	
	Odds Ratio (95% CI) (Unadjusted)	*p* Value	Odds Ratio (95% CI) (Unadjusted)	*p* Value
Monthly family income (USD)				
Above 150	*Reference*			
below 50	3.0 (1.5, 5.7)	**0.001**	1.3 (0.7, 2.4)	0.43
51–100	1.8 (1.0, 3.4)	0.06	1.2 (0.7, 2.2)	0.50
101–150	1.4 (0.7, 2.8)	0.34	1.1 (0.5, 2.0)	0.85
GMFCS level				
I	*Reference*			
II	1.3 (0.7, 2.6)	0.40	1.7 (0.9, 3.2)	0.11
III	1.6 (0.7, 3.4)	0.23	1.0 (0.4, 2.1)	0.93
IV	2.9 (1.4, 6.0)	**0.005**	1.9 (0.9, 4.0)	**0.08**
V	2.4 (1.1, 4.9)	**0.02**	2.1 (1.0, 4.3)	**0.04**
Intellectual impairment				
No	*Reference*			
Yes	1.3 (0.7, 2.3)	0.35	2.0 (1.1, 3.5)	**0.02**
Hearing impairment				
No	*Reference*			
Yes	1.9 (0.5, 7.3)	0.35	1.3 (0.3, 4.9)	0.72
Visual impairment				
No	*Reference*			
Yes	1.5 (0.6, 3.4)	0.35	1.6 (0.7, 3.6)	0.26
Speech Impairment				
No	*Reference*			
Yes	0.8 (0.5, 1.4)	0.48	0.7 (0.4, 1.1)	0.13
Neurological type of CP [1]				
Mono/hemiplegia	*Reference*			
Diplegia	1.2 (0.4, 3.2)	0.70	1.2 (0.4, 3.3)	0.69
Quadriplegia	1.2 (0.7, 2.1)	0.01	1.4 (0.8, 2.5)	0.23
Dyskinesia	1.3 (0.4, 3.9)	0.68	1.8 (0.6, 5.4)	0.30

[1] There were no triplegic child and one Ataxic child in our cohort. Due to the smaller size, we have excluded these two categories from this unadjusted analysis. The *p* values for statistically significant differences are shown in bold.

4. Discussion

Our novel study findings derive from an active hospital-based surveillance system and provide valuable insights on the burden and risk factors for malnutrition among children with CP in Vietnam. The proportion of children with malnutrition among our study cohort (i.e., 29% underweight and 30% stunted) was significantly higher than that reported in the general child population in Vietnam but lower than in other LMICs [10,14,25]. The reported burden of underweight from recent studies conducted in Bangladesh, Uganda and Ghana was 70%, 42% and 65% respectively [10,13,14] Our study utilized data from a hospital-based surveillance system. Considering the potential risk of representation bias of such a recruitment strategy, our findings may be an underestimate of the true burden of malnutrition among children with CP in Vietnam.

Vietnam has observed a steady improvement in the nutritional status of children over the past decade. The health policy and strategy framework of Vietnam demonstrates a commitment to reducing the burden of malnutrition among young children [26] The National Nutrition Strategy (NNS) of Vietnam (2011–2020) envisions a substantial reduction in malnutrition among children by the year 2020, aligning with the sustainable development goals (SDGs) [27] The cardinal role of nutrition in the

maintenance of health and wellbeing is well recognized and is demonstrated further by the emphasis on nutrition in the SDGs, particularly goals 1, 2 and 3. Following the launch of the NNS the Vietnamese government introduced several multisectoral initiatives including nutrition specific and nutrition sensitive intervention programs. The comparatively better nutritional status of children with CP in our study compared to those in other LMICs may be a result of these government initiatives to improve the nutritional outcomes of the population as a whole.

The characteristics of the malnourished children with CP identified through our active surveillance were similar to those from several other LMICs [10,13,14,25]. The majority of children in our study were from younger age groups. The significant association between age and underweight demonstrates the increased vulnerability of these young children to malnutrition as they get older. Similar findings were reported elsewhere [10]. Studies from other countries have also reported the relationship between malnutrition and age and motor severity of CP. Motor severity is likely to be associated with increased severity of oromotor dysfunction among children with CP, which acts as a barrier to self-feeding and/or adequate feeding. Evidence from HICs suggests that children with severe motor impairment for example, GMFCS level IV-V, often face difficulties with oromotor function [28,29]. These children also frequently have feeding difficulties such as choking, drooling, biting and gastro-esophageal reflux [2,3]. All these factors directly hamper regular food intake among these children. Studies also reported that children with severe motor impairment have altered energy requirements and body composition for example, reduced fat free mass, changes in total body fat [30]. This is consistent with our study findings, which revealed a significant association between the nutritional status of children with CP and motor severity and associated impairments.

It is evident that in the absence of appropriate interventions, children with CP are at high risk of developing malnutrition. In HICs, nasogastric tube feeding has been found to be beneficial for weight gain in children with CP [31]. However, this intervention is not widely available or utilized in LMICs, where there is aversion to increased risk of morbidity through adverse consequences for example, overfeeding, infection or aspiration [32]. Studies conducted in Bangladesh and Ghana demonstrate that improved nutritional status among children with CP can be achieved through training of caregivers with a specific focus on recommended feeding behavior [13,19].

Poor feeding practices such as incorrect positioning and nutritional inadequacy of the diet are often closely intertwined with the poor socio-economic status of families of children with CP. In our study, the burden of malnutrition among children with CP is higher among poorer families. This finding remained unchanged when adjustment was made for other socioeconomic and clinical characteristics. A similar pattern was observed in another LMICs [10]. The conceptual framework of malnutrition clearly shows that economic vulnerability directly and indirectly enhances the risk of malnutrition, comorbidity and mortality among children [9].

Study Limitations

Despite our considerable efforts, this study had limitations. First, it was a hospital-based study which imposed a potential risk for biased representation of children with CP in Vietnam. Thus, the findings must be interpreted with caution and consideration that the true scenario might differ from the reported findings. Second, we focused on selective anthropometric measurements to assess nutritional status. Although, utilization of other inexpensive anthropometric measurements for example, subscapular skinfold thickness, triceps skinfold thickness, mid upper arm circumference could provide more information of the overall nutritional status of children with CP, considering the availability of resources and to minimize errors in the data we only included the height and weight in this study. A detailed assessment, such as measurement of body fat, fat free mass or bone mineral density requires advanced technology for example, biometric impedance analysis, dual-energy X-ray absorptiometry. Assessment of the dietary intake pattern including caregiver's knowledge, capacity and practice regarding adequate feeding practices to the children with CP and detailed assessment of the level of oromotor dysfunction could potentially yield a better understanding of nutritional status

and establish possible causal relationships between risk factors identified in this study for example, socio-economic status, motor severity and malnutrition among children with CP. Third, we assessed the nutritional status of our study participants by comparing their anthropometric data to the WHO reference population. Recent evidence from HICs indicates that the growth curve of children with CP differs from the general population [33]. However, such CP specific and/or ethnicity specific data are not available for LMICs like Vietnam. Nevertheless, the method utilized in our study for the assessment of nutritional status is widely accepted in these settings.

5. Conclusions

Global evidence shows that malnutrition increases the risk of morbidity and mortality among children. This is intensified when malnutrition is accompanied by a disability such as CP. Although evidence from different countries has identified few common risk factors for malnutrition among children with CP, the burden and intensity is highly influenced by contextual factors. Considering the dearth of available evidence from LMICs, our study has generated new data that add substantially to current knowledge about the nutritional status of children with CP in Vietnam. These findings will guide the development of evidence-based training for health professionals and interventions for children with CP in Vietnam.

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5.4 CHAPTER SYNOPSIS

In this chapter, findings regarding children with CP from another LMIC, Vietnam, have been described. These studies used a different epidemiological tool, hospital-based surveillance, to collect data from Vietnam. Although not population representative, these studies have generated valuable data on children with CP.

The children with CP in Vietnam predominantly had spastic CP (95.2%). Most (69.6%) were quadriplegic and 60.3% were GMFCS level III-V. 28.9% underweight and 29.0% stunted; children with quadriplegia, GMFCS level IV to V and/or aged >5 years were more vulnerable to malnutrition. These findings will inform clinical practice and policy in low resource settings, particularly in hospital-based settings.

Detailed discussion on the implications of these findings and the overall thesis are described in the following section.

DISCUSSION AND RECOMMENDATIONS FOR PRACTICE, POLICY AND RESEARCH

In this section, the findings from the doctoral research and their bearing on practice, policy and research are discussed.

THESIS SUMMARY: BRIDGING THE GAPS

The overall aim of this thesis was to describe the clinical characteristics of CP, with concurrent exploration of measures for early identification and intervention for children with CP in low resource settings. The areas covered in the thesis in relation to each of the specific aims of the thesis are outlined below,

Aim (i) better understand the clinical characteristics of children with CP in Bangladesh with a specific focus on hip dysplasia and epilepsy

> Hip dysplasia and epilepsy among children with CP in Bangladesh have been described in *Chapters 1 and 2.* The BCPR served as the sampling frame for both the studies.

Aim (ii) explore pathways to improve age at diagnosis of CP in Bangladesh

> *Chapter 3* delineates pathways for early diagnosis of CP in Bangladesh. It includes a publication outlining current practice and eludes into the future of early diagnosis of CP in LMICs.

Aim (iii) enhancing interventions for children with CP and their primary caregivers in Bangladesh through a quasi-experimental study assessing the outcome of an existing program in Bangladesh

> *Chapter 4* describes the outcome of an existing intervention program for children from BCPR. In additional to the child outcomes i.e. motor, speech and communication, this study reports the wellbeing of the primary caregivers.

Aim (iv) describe CP in another low resource setting using an alternative epidemiological tool through a hospital-based surveillance in Vietnam

> *Chapter 5* describes that state of evidence on CP in another LMIC, Vietnam. This chapter includes description of clinical characteristics, aetiologies, rehabilitation, education, and detailed nutritional status of children with CP through a hospital-based surveillance modelled on Paediatric Active Enhanced Disease Surveillance (PAEDS).

CEREBRAL PALSY REGISTERS IN LOW RESOURCE SETTINGS

CP registers are emerging in LMICs and the ensuing increased availability of data from low-resource settings has advanced our knowledge on CP substantially.(4, 33, 48, 49). The findings from recent studies in Nepal, Indonesia and Uganda confirm a marked contrast to the data from HICs.(22, 50, 51) In LMICs, the prevalence of CP is higher, diagnosis is delayed, there is an overwhelming number of children with greater motor severity of impairment, the burden of associated impairments is high, few have access to education and rehabilitation.(4, 14, 51) The rates of the prevailing aetiologies and risk factors in LMICs (i.e. intrapartum related neonatal respiratory depression, neonatal encephalopathy, neonatal jaundice, infections) differ considerably from the HICs that have realized tremendous success in reducing the rates of CP by addressing such factors.(50, 52) Thus, reaffirming that prioritization of equitable access to quality perinatal care for effective prevention of CP is imperative.(15)

BANGLADESH CERERBAL PALSY REGISTER: ONWARDS AND UPWARDS

The BCPR study and the translational research facilitated by it demonstrates the tremendous potential CP registers hold, even in low resource settings. Since the publication of the BCPR study findings in 2019 described previously in this thesis,(33) the study activities have been expanded across six districts of Bangladesh to include 3135 children with CP to date with view of developing a national CP register; updated findings from the ongoing surveillance have been reported in two recent publications.(4, 53). The BCPR has served as the sampling frame for three studies described in *Chapters 1,2 and 4* of this thesis.(54). Since its inception in 2015, it has additionally enabled the conduct of a range of studies reporting immunization, nutrition, rehabilitation, health related quality of life and sexual wellbeing of children and adolescents with CP and their primary caregivers in Bangladesh.(40, 55-59). Furthermore, the BCPR has facilitated local capacity building and continues to foster emerging researchers in an important area. In addition to this thesis, the expansive work related to the BCPR study has resulted in the following doctoral research,

- Adolescents with cerebral palsy in rural Bangladesh: Health-related quality of life, mental health and sexual and reproductive health |*Dr Rosalie Power, University of Sydney (PhD completed)*

- The epidemiology, prevention and control of malnutrition among children with Cerebral Palsy in low- and middle-income countries│ *Israt Jahan, final year PhD student, CQUniversity*

- Developing a sustainable model of early intervention and rehabilitation service for children with CP in LMICs: translational research using the Global LMIC CP Register│ *Mahmudul Hassan Al Imam, final year PhD student, CQUniversity*

The BCPR has enabled generation of high quality population-based data which is the one of the best sources of data for epidemiological exploration.(24) and enabled estimation of prevalence and extrapolation at national level.(33) Such information is invaluable to program planning and policy development through an evidence-based approach.

HOSPITAL-BASED SURVEILLANCE IN VIETNAM: NEXT STEPS

Methodological differences need to be accounted for in interpretation and comparison of study findings from different parts of the world.(6) In contrast to Bangladesh, the findings from the hospital-based surveillance show a glimpse of common risk factors and clinical characteristics among children with CP in Vietnam. Although not population representative, these findings provide the necessary baseline for further exploration in hospital-based settings which is often the ideal setting for certain strategies for prevention, diagnosis, and intervention for CP. The PAEDs system on which this surveillance is modelled enabled data collection as part of routine services through an opportunist purposive recruitment strategy and can be easily scaled up to generate best available data in absence of population data.(60)

The findings and the ongoing collaboration through the studies outline in *Chapter 5* have stimulated further research in Vietnam. This has resulted in an upcoming project titled, 'Evidence based approach to surveillance, early diagnosis and intervention of children with cerebral palsy in Vietnam' [Research Foundation of Cerebral Palsy Alliance: PRG08419, Grant amount: AU$200,230.00 over 3 years]. As one of the chief investigators on this study, I aim to build on my doctoral research in Vietnam through this project as part of my postdoctoral research. The broader vision is to replicate the successes in early detection of CP reported in HICs. This will complement the ongoing national efforts in Vietnam, including the

implementation of the National Rehabilitation Guideline for the Management of Children with CP (https://hivndrive.wixsite.com/hivn/rehabguidelines).

ASSOCIATED IMPAIRMENTS

Although CP is defined as a motor disability, it is commonly associated with a range of impairments.(61) A systematic review on the clinical prognostic messages for CP outlines, "Among children with cerebral palsy, 3 in 4 were in pain; 1 in 2 had an intellectual disability; 1 in 3 could not walk; 1 in 3 had a hip displacement; 1 in 4 could not talk; 1 in 4 had epilepsy; 1 in 4 had a behavior disorder; 1 in 4 had bladder control problems; 1 in 5 had a sleep disorder; 1 in 5 dribbled; 1 in 10 were blind; 1 in 15 were tube-fed; and 1 in 25 were deaf".(62) While it is important to address each of these concerns for children with CP and their families, the following discussion and recommendations focus on the associated impairments described in detail in this thesis i.e. hip dysplasia (*Chapter 1*), epilepsy (*Chapter 2*), and malnutrition (*Chapter 5*).

Hip dysplasia

Hip displacement often results in progressive functional limitation.(63) However, with timely detection and intervention, this can be prevented and the secondary complications, such as hip dislocation, pain, functional limitations, and poor quality of life, can be reduced;(64) through period clinical examinations and radiography i.e. routine hip surveillance among children with CP.(65) There are now established clinical guidelines for hip surveillance among children with CP.(64) The hip surveillance program in Sweden demonstrated the impact of hip surveillance i.e. improved wellbeing of children with CP and their families, and has virtually eradicated hip dislocation among children with CP.(66)

The Australian hip surveillance guideline has been rationalized recently informed by temporal data. It informs the frequency of radiographic examination among lower risk groups and the continuation of surveillance into adulthood for adolescents with identified risk factors.(64, 67, 68) This reaffirms the importance of monitoring temporal trends in hip dysplasia to inform clinical practice and interventions for CP. Chapter 1 of this thesis provides baseline data that will inform the establishment of a hip surveillance program in Bangladesh and other low

resources settings where similar patterns of motor severity of CP and hip dysplasia are observed.(4, 54)

Epilepsy

Poor epilepsy control results in poor health outcomes for children with CP and greater caregiver burden.(69) As outlined in *Chapter 2* epilepsy control among children with CP is challenging. This is particularly challenging in remote settings where retention of qualified/trained health professionals in poor.(70) Therefore, as an extension of the work described in Chapter 2, a simple guideline for epilepsy management among children with CP has been developed and translated to local language (Appendix B). The aim is to make the guideline available to physicians and supporting health workers in remote settings in Bangladesh to ensure better epilepsy control even in absence of highly skilled professionals.

Furthermore, intellectual impairment is common in children with epilepsy and CP. Antecedents of epilepsy and intellectual impairment overlap and often reflect greater severity of brain injury and motor impairment.(71) Both epilepsy and intellectual impairment have significant bearing on long-term prognosis, education, employment, social integration and overall wellbeing of individuals with CP.(72, 73) Further research into management of these related conditions through a comprehensive life-course health development approach in low resource settings is essential.

Malnutrition

Malnutrition among children with CP is compounded by a range of risk factors and associated impairments.(74) Poor nutritional status is often both a cause and consequence of more severe outcomes of CP. Malnourished children with CP are also at greater risk of mortality.(75) Nutritional interventions need to be integrated into regular medical check-ups and rehabilitation programs for children with CP and tailored to address the impact of the co-occurring conditions and heterogeneity of CP. Development of caregiver knowledge and capacity is instrumental to the maintenance of optimum nutritional status among children with CP, particularly in LMIC settings.(76, 77) Due to prevailing health inequities and their

impact on access to services,(78) such equity focused intervention approaches are warranted in low resource settings.

EARLY DETECTION

The 2017 clinical guideline on the early diagnosis of CP outlines best practice tools to support diagnosis.(79, 80) It states that it is now possible to accurately diagnose CP before six months' corrected age through a combination of evidence-based tools, i.e., General Movements Assessment and Hammersmith Infant Neurological Examination, and neuroimaging. Although there have been remarkable strides made in the sphere of early diagnosis of CP in the past decade, there is an increasing shift towards ensuring intervention as soon as a child is identified to be at risk of CP.(47) An interim high risk of CP clinical diagnosis is recommended when confirmation of diagnosis is delayed.(46) With earlier diagnosis and the availability of the latest international clinical practice guideline for intervention for children younger than two years with or at risk of CP, there is tremendous potential to harness neuroplasticity to enhance function and participation of children with CP.(81) There is a dire need for local capacity building to integrate the use of these tools within the existing structures in LMICs.

Finding from BCPR show that diagnosis of CP is substantially delayed in Bangladesh. Similar patterns have been reported in studies from other LMICs.(48, 82) This is unsurprising in absence of the use of GMA, HINE and neuroimaging in these settings. In contrast to HICs, diagnosis of CP in LMICs is delayed beyond the period when children with CP show early signs of activity limitations and associated delay in developmental milestones from six months of age.(83) In HICs waiting for delayed motor developmental milestones may be too late. This however is often the first sign of concern for parents of children with CP. The DMC described in *Chapter 3* can therefore serve as a valuable screening tool to ensure referral for detailed clinical assessment by a qualified clinician for an interim high risk of CP clinical diagnosis based on risk factors and clinical presentation. With the increasing shift towards identification of "at risk" of CP to ensure early intervention within the period of optimum neuroplasticity, further research to explore the feasibility of the widely used criteria for the interim high risk of CP clinical diagnosis in low resource settings is needed.

These efforts however are not a substitute to the best practice clinical guidelines.(46) Contemporaneous efforts to support the implementation of the use of GMA, HINE, and neuroimaging for early accurate diagnosis of CP must be made in LMICs. My postdoctoral research will explore the feasibility of the use of these tools in low resource settings. This work will utilise data from an ongoing study titled, *Early Detection and Early Natural History of Cerebral Palsy in Bangladesh*, and an upcoming study titled, *Evidence based approach to surveillance, early diagnosis and intervention of children with cerebral palsy in Vietnam.* Both studies are an extension of the ongoing collaborations in Bangladesh and Vietnam and are funded by the Research Foundation of Cerebral Palsy Alliance. These studies are expected to support the development of a cost-effective scalable model for early detection of children with CP in low resource settings.

EARLY INTERVENTION

As outlined previously, delayed diagnosis is one of the major barriers to early intervention in LMICs. This further contributes to poor outcomes for children with CP and the caregiving burden of the families. In *Chapter 4*, outcomes of a community-based intervention program for children identified with CP have been assessed and described through a quasi-experimental study. Although, the findings from this quasi-experimental study are promising, further exploration through a randomized controlled trial is needed. This work underpins the need for such caregiver led community-based rehabilitation program for children with CP in LMICs such as Bangladesh, particularly in the rural settings, where services and trained health workers are scarce.(70)

LIMITATIONS AND STRENGTHS

Specific limitations and strengths of each study have been discussed in the publications included within the thesis in *Chapter 1,2,3,4* and *5*. Here, the limitations and strengths of the overall thesis is described.

Firstly, one of the major challenges of a population-based surveillance is attainment of complete case ascertainment. When conducted conventionally over a short period of time, KIM has a 77.6% case ascertainment rate compared to door-to-door survey for identification

of children with physical impairments such as CP in LMICs.(37) However, it is likely that majority of children living with CP in the BCPR surveillance area during the collection of baseline information for the BCPR have been identified due to the continuing engagement of the CSF Global team on site for a range of research projects and services. Secondly, diagnosis of CP is substantially delayed, it is likely that complete ascertainment has not been possible for children with CP below the average age of diagnosis of CP. Furthermore, mortality is high among children with CP in LMICs.(75) A substantial proportion of children with CP, particularly those with more severe CP, would have had premature deaths before being enrolled in the CP register which limits accurate identification of etiological factors. Thirdly, confirmation of precise diagnosis and description of CP is challenging among children under the age of five years due to the changes in the clinical presentation and CP subtype during this period. Fourthly, a proportion of children with mild CP may not have been identified for inclusion in both the methods described; In Bangladesh, KIM may have missed children with mild CP and in Vietnam, children with mild CP may not have presented at the hospital-based services.

Important strengths of this doctoral research are that it describes high quality data from two robust methods. Studies from Bangladesh use the BCPR, a population-based surveillance as the sampling frame, therefore generating best available epidemiological data. The BCPR has served as sampling frame for several observational studies and RCTs. These have been an indelible contribution to the knowledge base on CP in LMICs. In contrast, the hospital-based surveillance in Vietnam is modelled on a highly successful method in Australia, the PAEDS mechanism. This method can potentially be utilized for the surveillance of other conditions and is therefore a valuable epidemiological resource for studies with aims from the BCPR studies. Existing hospital settings are often ideal sites for piloting approaches novel to different parts of the world. This can be achieved through integration of evidence-based approaches to early detection and intervention for children with CP in regular medical check-ups and available health services in hospitals. Therefore, baseline hospital-based data is the necessary first step towards this vision.

OVERALL RECOMMENDATIONS FOR PRACTICE, POLICY AND FUTURE RESEARCH

Global Low-and Middle-income country CP Register (GLM-CPR) is the first multi-country epidemiological exploration of data on children with CP in LMICs.(4) Findings from the GLM-CPR reaffirm the urgent need for identification and implementation of appropriate strategies for prevention, early detection, and intervention for children with CP in LMICs. Greater motor severity of CP has been reported from LMICs across the world. This is linked to a range of factors including delayed diagnosis, delayed intervention, poor access to rehabilitation services, unmet equipment needs and the interplay of a myriad of socioeconomic factors with the severity of impairments.(4, 53)

With the advent of understanding of the etiopathogenesis of CP, there are now clear pathways for prevention of CP.(84-86) There is ample evidence on evidence-based approaches to early detection and intervention for children with CP.(46, 81) There is documented success from HICs with long standing CP registers and related programs e.g. perinatal care for prevention of CP to reduce incidence(15) and hip surveillance programs to avert complications.(64) There is an urgent call for action to extend the implementation of the numerous proven strategies to LMICs. International multidisciplinary efforts are warranted to address the global burden of CP with the shared vision to prevent CP and support individuals living with CP and their families with an equity focused approach.

There is an increasing focus on neurological interventions for CP with the recent advances in the knowledge on neuroplasticity of the developing brain.(3) However, as a lifelong condition, the approach to interventions for CP need to be through a life-course perspective.(2) As described by Chabrier et al, ''This new paradigm should guide individual, familial and collective care interventions and research strategies beyond the scope of CP''.(87) Further research is needed in the spheres of school readiness, employment, and social integration to ensure that children with CP can grow up to be adults with future opportunities, dignity, and meaningful relationships. Supporting the often-overlooked families and caregivers of individuals with CP, who bear the majority of the caregiver burden, particularly in low resource settings, will also be instrumental to this vision.

> *Summary of recommendations of practice, policy and future research*
>
> - Surveillance of CP in LMICs to identify gaps, monitor temporal trends, facilitate further research, and rationalize guidelines for low resource settings
>
> - Equity focused approach to prevention, early diagnosis and intervention for CP and common associated impairments such as hip dysplasia and epilepsy
>
> - Promotion of true disability inclusive development through a life course approach to ensure best outcomes and wellbeing of individuals with CP into adulthood
>
> - Interventions to support families and caregivers of individuals living with CP who bear majority of the burden, particularly in low resource settings
>
> - Foster international collaborations and knowledge transfer to address the global burden of CP as a shared goal.

CONCLUSION

This thesis provides valuable data for a better understanding of CP and maps the path towards the establishment and use of national CP registers in low resource settings. Strategies for early detection and a promising early intervention program for children with CP and their families in Bangladesh, a typical LMIC, have also been described. Furthermore, using hospital-based surveillance, the clinical characteristics of children with CP have been reported in Vietnam. This doctoral research identified important knowledge and service gaps for children with CP and their families in LMICs and addressed some of them.

The gradually increasing shift of focus towards countries where the burden of CP is higher and greater risk prevails; the reported decline of prevalence, severity, and co-occurring conditions in HICs; and the emerging CP registers and research in LMICs is encouraging. There are reasons to be optimistic that these changes will be coupled by the incorporation of preventive, diagnostic and rehabilitation efforts in LMICs while the search for a cure for CP continues. With concerted efforts the successes observed in HICs can be replicated in low resource settings with a shared vision to address the global burden of CP.

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Epidemiology of cerebral palsy in Bangladesh: a population-based surveillance study

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AIM To examine the prevalence, clinical characteristics, and risk factors of cerebral palsy (CP) in children in Bangladesh.

METHOD The Bangladesh CP Register is an ongoing population-based surveillance database of children with CP from a geographically defined area in Bangladesh. Cases were defined based on Surveillance of CP in Europe and Australian CP Register criteria after clinical assessments and identification by the key informant's method.

RESULTS In total, 726 children with CP were identified between January 2015 and December 2016. Mean age was 7 years 7 months (standard deviation [SD] 4y 6mo; range: 4.8mo–18y; median 7y 1.2mo; 61.8% male, 38.2% female). Mean age at CP diagnosis was 5 years 2 months (SD 3.8). Observed prevalence was 3.4 per 1000 children (95% confidence interval [CI]: 3.2–3.7), resulting in an estimated 233 514 children (95% CI: 219 778–254 118) with CP in Bangladesh. The majority (79.6%) had spastic CP. Altogether, 79.6% of the children with CP had at least one associated impairment (speech 67.6%, intellectual 39.0%, epilepsy 23.7%, visual 10.2%, and hearing 10.2%). In total, 78.2% never received rehabilitation.

INTERPRETATION In Bangladesh, the burden of CP is high, and diagnosis is substantially delayed, limiting opportunities for early intervention. There is a lack of available services and the majority of the children had preventable risk factors.

Cerebral palsy (CP) comprises a heterogeneous group of early-onset, non-progressive, neurodevelopmental disorders caused by insult to the developing brain.[1] CP is a leading cause of disability among children, with a prevalence of approximately 2 per 1000 live births. Globally, there are an estimated 17 million people living with CP.[2] The epidemiology of CP has been studied extensively in high-income countries (HICs). However, in low- and middle-income countries (LMICs), there is paucity of evidence based on large, general population-representative samples, which can provide reliable, unbiased data.

A recent systematic review and meta-analysis of prevalence of CP included 49 studies, of which 46 were conducted in HICs.[3] Out of the three studies from LMICs, only one (from China) used a population-based sample of children aged younger than 7 years and reported a prevalence of 1.6 per 1000 children.[4] Most studies of children with CP in LMICs are based on high-risk groups from hospital or specialist clinic samples.[5] A recent population-based study of CP in Uganda, using a health and demographic surveillance system, showed a prevalence of CP of 2.7 (95% confidence interval [CI] 2.2–3.3) per 1000 children.[6] General population-based studies are therefore needed to accurately quantify the prevalence of CP in LMICs, which is crucial for health service planning.

The clinical characteristics of and risk factors for CP in LMICs may differ from those in HICs.[5,7,8] Preterm birth is a leading risk factor in HICs.[9] However, a study based on rehabilitation clinic attendees suggested the proportion of children with CP in Bangladesh born preterm is much lower than that in Australia (18.5% vs 42.9%).[10]

Moreover, CP continues to be commonly attributed to a range of perinatal and birth-related factors, such as birth asphyxia, in LMICs.[11,12] Additionally, the role of infections in the aetiology of CP and relevant preventive strategies are being increasingly explored, and are pertinent in low-resource settings where they continue to be more prevalent.[13]

In a recent study, signs of neonatal encephalopathy were more common among children with CP in Bangladesh than in Australia.[10] Similarly, a hospital-based study from Nigeria

reported that birth asphyxia, bilirubin encephalopathy, and postinfectious brain damage were the main causes of CP.[14] As access to specialist care is limited for children with CP in LMICs, studies based on clinical samples may not be representative of all children with CP. There may be systematic differences between those who can and cannot afford rehabilitative services. Therefore, large population-based studies are needed to investigate the clinical characteristics and risk factors for children with CP in LMICs.

In the last 30 years, general population-based registers and surveillance programmes have facilitated comprehensive studies into the epidemiology of CP.[15–18] The main aims of these initiatives are to monitor incidence and prevalence of CP, understand comorbidities and risk factors, design and evaluate preventative strategies, and monitor service delivery.[15,17] To the best of our knowledge, there are currently 38 established CP registers/surveillance programmes worldwide, none of which are in LMICs.[19]

We examined the prevalence, clinical characteristics, associated impairments, risk factors, and service utilization in children with CP in rural Bangladesh through the first general population-based CP register in a LMIC, the Bangladesh Cerebral Palsy Register (BCPR).

METHOD
The BCPR is an ongoing population-based surveillance programme that includes children (recruited before 18y of age) with a confirmed clinical diagnosis of CP, living in a geographically defined area in a northern subdistrict of Bangladesh (i.e. Shahjadpur) with a known denominator population. There are 296 villages and an estimated 70 998 households with a total population of 561 076 (child population 226 114),[20] and 12 117 live births per annum.[21] Baseline case identification for the register took place between January 2015 and December 2016, which forms the BCPR cohort.

Participants
Cerebral palsy was defined based on Surveillance of CP in Europe[22] and Australian CP Register[15] criteria. Children were identified by the community-based key informant's method[23,24] and then assessed in a subsequent clinic. A detailed account of the BCPR study has been described previously.[20]

Screening and identification of children with suspected CP
The key informant's method involves training of local volunteers, referred to as key informants, who reside in the community.[20] It is a novel method that was developed to identify children with blindness in LMICs.[23] Subsequently, the key informant's method was successfully used to identify children with other impairments in LMICs and was found to be sensitive and highly cost-effective.[24] The study implementation team (CSF Global; www.csf-global.org) has an extensive network of trained key informants in the surveillance area. For this study, two trained community

What this paper adds
- Prevalence of cerebral palsy (CP) is 3.4 per 1000 children in rural Bangladesh.
- There are an estimated 233 514 children with CP in Bangladesh.
- The majority have potentially preventable risk factors.
- Diagnosis of CP is delayed, limiting opportunities for early intervention.
- There is a lack of available services for children with CP in rural Bangladesh.

mobilizers were engaged for identification of the key informants in the study area. The key informants received day-long structured training on the identification of children with suspected CP. After initial training, key informants identified and listed potential cases in their communities and informed the families of the date and venue of the medical assessment camps, which were conducted regularly in the study area. The children underwent clinical assessment for confirmation of the diagnosis of CP before registration into the BCPR.[20]

Multidisciplinary medical assessment
A detailed neurological assessment was performed by a multidisciplinary medical assessment team comprised of a paediatrician, a physiotherapist, and a counsellor. The BCPR registration form, a modified version of the Australian CP Register record form (Appendix S1, online supporting information), was used to collect information on pregnancy, birth history, and sociodemographic factors. Gestational age was estimated based on last menstrual period, patient's history, and limited available medical records. Neurological types of CP, along with Gross Motor Function Classification System (GMFCS)[25] and Manual Ability Classification System (MACS)[26] levels, were assessed. MACS was determined for children over 4 years of age. Anthropometric measurements – weight (kg) and height (cm) – were also measured using standard measuring instruments and following standard guidelines. Z-scores for weight for age, height for age, and weight for height were calculated using the standard formula. Detailed methods and the nutritional status of our cohort has been reported previously.[27]

The presence and severity of comorbidities (i.e. epilepsy, visual, hearing, speech, and intellectual impairments) was documented based on review of any previous medical records, report by the parents or primary caregivers of the children with CP, and clinical assessment. Parents or primary caregivers were asked specific questions regarding the presence of each of the associated impairments and subsequent clinical history was taken, and detailed assessment was conducted by clinicians to determine the type and severity of associated impairments.

Diagnosis of epilepsy was based on the history of one or more unprovoked seizure in the previous 3 months beyond the neonatal period. Assessment was based on clinical history taken by medical practitioner and review of any available medical records of relevance.

Assessment of intellectual impairment was based on history taken by the medical practitioner from the primary caregiver and review of any available medical records.

Visual impairment was determined through history, available medical records, and clinical assessment of visual acuity and functional vision, including counting fingers, hand motion, and light perception. A monocular cover–uncover test was conducted for determination of strabismus.

Assessment of hearing impairment was based on hearing-related medical history, including child's response to name call, clap and vehicle horns, previous ear infections, symptoms of ear pain or drainage, family history of hearing loss, prescription and over-the-counter medication history, and previous use of hearing loss interventions. Otoscopic examination was performed to evaluate the pinna (outer ear), external auditory canal, and tympanic membrane for any conditions that could be contributing to hearing loss or that may require further evaluation and treatment, such as cerumen impaction and abnormality of the tympanic membrane.

Assessment of speech was based on history taken from primary caregiver and detailed speech and language assessment by medical practitioner. Expressive and respective language, naming quality, and quality of conversational speech were also observed.

Intrapartum-related neonatal respiratory depression was defined as a newborn failing to cry at the time of birth, experiencing delayed onset of breathing (>1min), or requiring assistance to initiate breathing (ranging from drying, stimulation, and milking of the umbilical cord to mouth-to-mouth breaths). Probable intrapartum-related neonatal respiratory depression was defined as neonatal respiratory depression among infants born at term without congenital malformations.[28]

Early feeding difficulty was considered when a neonate was unable to breastfeed in the first month of life owing to poor sucking ability.

Neonatal encephalopathy was defined as a 'disturbance of neurological function in the earliest days of life in the term infant manifested by difficulty initiating and maintaining respiration, depression of tone or reflexes, abnormal level of consciousness and often by seizures'.[29] Possible neonatal encephalopathy was defined based on neurological abnormalities observed in the first 7 days of life (seizures or lethargy and early feeding difficulty).[28]

Neonatal sepsis was defined as 'a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life'.[30]

Comparison between the BCPR cohort and the general population of the surveillance area was conducted using National Population and Housing Census, which collects data on demographic and health indicators nationally up to subdistrict level.[21,31] The demographics and known maternal and perinatal risk factors for CP were also compared with local and national data for the general population.

Ethical considerations

Ethical approval was obtained from the Cerebral Palsy Alliance Human Research Ethics Committee (EC00402; ref no. 2015-03-02) in Australia; the Asian Institute of Disability and Development Human Research Ethics Committee (southasia-irb-2014-l-01); and the Bangladesh Medical Research Council Human Research Ethics Committee (BMRC/NREC/2013-2016/1267) in Bangladesh. Written informed consent was obtained from parents or primary caregivers of all the study participants.

Statistical analysis

Descriptive (mean, median, and proportion) and bivariate (χ^2, Fisher's exact test, and independent-sample t-test) analyses were carried out. A p value of less than 0.05 was considered significant. Data were analysed using SPSS Statistics software version 23 (IBM, Armonk, NY, USA).

The observed prevalence of CP was estimated by dividing the total number of children with CP by all live births in the surveillance area between 1998 and 2016.

Prevalence of CP by gestational age was estimated only in children aged 5 years of age or older. Children aged younger than 5 years (i.e. born after 2011) were excluded from the analysis, as diagnosis of CP in young children is difficult and less precise than that of older cohorts,[32] and could give an underestimate because of incomplete case ascertainment. The total number of live births between 1998 and 2011 in the surveillance area was derived from the Bangladesh Population and Housing Census data.[21] The proportion of births across gestational age groups was used to determine the total number of live births across the gestational age groups.[31] The prevalence of CP across each gestational age group was then determined by dividing the number of children living with CP by the total number of live births in respective gestational age group in the surveillance area between 1998 and 2011.

RESULTS

During the study period, 847 children with suspected CP were assessed, of whom 726 (85.7%) had a clinical diagnosis of CP and were recruited into the BCPR. Herein, we describe all cases of CP identified in the surveillance area.

The mean age of study participants was 7 years 7 months (standard deviation [SD] 4y 6mo; range: 4.8mo–18y; median 7y 1.2mo; interquartile range 3y 8.4mo); 61.8% (n=449) were male, 38.2% (n=277) were female. The mean age at CP diagnosis was 5 years 2 months (SD 3y 9.6mo); this varied significantly between semi-urban (4y 4mo [SD 3y 2.4mo]) and rural (5y 5mo [SD 4y]) areas (p<0.005). In total, 17.6% (n=128) children were diagnosed within the first 1000 days of life, of whom 95.3% (n=122) were diagnosed during the assessment camps as part of this study. Table I demonstrates the baseline characteristics, predominant CP subtypes, functional motor severity classifications, and associated impairments of the BCPR cohort.

The mean monthly income of the families was 103.9 US dollars (USD) (SD 86.2USD; median 72.0USD, interquartile range 72.0–120.0USD). In total, 97.2% of the families included in the CP register were living below the poverty line (i.e. daily income per capita <1.90USD),[33] which is

Table I: Baseline characteristics, predominant cerebral palsy (CP) subtype, functional motor severity classifications, and associated impairments of the children with CP recruited into the Bangladesh Cerebral Palsy Register (n=726)

Characteristics	BCPR
Sex	
Male	449 (61.8)
Female	277 (38.2)
Age group (y)	
<5	248 (34.2)
5–9	263 (36.2)
10–14	155 (21.3)
15–18	60 (8.3)
Predominant CP motor type and subtype	
Spastic	578 (79.6)
Monoplegia/hemiplegia	198 (27.3)
Diplegia	124 (17.1)
Triplegia	70 (9.6)
Quadriplegia	186 (25.6)
Hypotonic	87 (12.0)
Dyskinetic	60 (8.3)
Ataxic	1 (0.1)
GMFCS level	
I	98 (13.5)
II	133 (18.3)
III	157 (21.6)
IV	172 (23.7)
V	166 (22.9)
MACS level[a]	
I	116 (21.5)
II	92 (17.0)
III	97 (18.0)
IV	111 (20.6)
V	124 (23.0)
Associated impairments[b]	
Speech	487 (67.1)
Intellectual	281 (38.7)
Strabismus	207 (28.5)
Epilepsy	170 (23.4)
Hearing	74 (10.2)
Visual	73 (10.1)

Data are n (%). [a]Manual Ability Classification System (MACS) was applicable for 540 children ≥4y. [b]Multiple impairments were reported for several children. GMFCS, Gross Motor Function Classification System.

significantly higher than the national average (18.5%; p<0.001).

Prevalence of CP

In the surveillance area the observed prevalence of CP was 3.4 per 1000 live births (95% CI: 3.2–3.7) from 1998 to 2016. Based on this prevalence we estimate that there are 233 514 children with CP in Bangladesh (95% CI: 219 778–254 118), based on 68 680 562 live births in Bangladesh from 1998 to 2016.

The observed prevalence of CP varied by sex and area of residence; prevalence was higher in males than females (χ^2=29.4; p<0.001); 3.7 per 1000 males (95% CI: 3.4–4.1) and 2.5 per 1000 females (95% CI: 2.2–2.8). The observed prevalence was 4.7 per 1000 children in semi-urban (95% CI: 3.9–5.6), and 2.9 per 1000 children in rural (95% CI: 2.7–3.2) parts of the surveillance area (χ^2=16.738; p<0.001).

Birth prevalence of CP by gestational age in children aged 5 years or older

The prevalence of CP varied by gestational age; the highest prevalence was observed to be 7.8 per 1000 live births (95% CI: 5.6–10.9) for those born very preterm (28–31wks' gestation). The prevalence of CP was 1.1 per 1000 live birth (95% CI: 0.5–2.4) and 1.6 per 1000 live births (95% CI: 1.2–2.2) for those born at 32 weeks to 33 weeks and at 34 weeks to 36 weeks respectively (Table II).

CP motor type and functional motor severity classifications

The majority of the children (79.6%; n=578) had a spastic motor type; 27.3% (n=198) had monoplegia/hemiplegia, 17.1% (n=124) had diplegia, 9.6% (n=70) had triplegia, and 25.6% (n=186) had quadriplegia. In total, 68.2% (n=495) were described as GMFCS level III to V; 61.5% (n=332) of the children were MACS level III to V (Table I).

Associated impairments

In total, 79.6% (n=578) of the children had at least one associated impairment. Altogether, 67.1% (n=487) had speech impairments, including 35.1% (n=253) who were non-verbal. Two hundred and eighty-one (38.7%) had an intellectual impairment, 28.5% (n=207) had strabismus, 23.4% (n=170) had epilepsy, 10.2% (n=74) had hearing impairment, and 10.1% (n=73) had visual impairment, including 3.9% (n=28) who were functionally blind. Children with CP had a significantly higher rate of associated impairments compared with the general population (p<0.001; Table III).

Risk factors

Prenatal and perinatal risk factors were reported for 61.6% (n=447) of children, including intrapartum-related neonatal respiratory depression, neonatal encephalopathy, and infections (e.g. neonatal sepsis, pneumonia, central nervous system infection, such as meningitis and encephalitis). Post-neonatal factors were reported for 6.1% (n=44), which included infection (e.g. pneumonia and sepsis), drowning, and trauma.

Mean maternal age at birth was 22 years and 2 months (SD 6y 6mo; median 20y 10.8mo; range 13–42y). In total, 40.1% (n=291) of mothers were illiterate versus the national average of 25.0% (p<0.001). Only 30.3% (n=220) of mothers received regular antenatal care. The majority (72.7%; n=528) of the children were delivered at home, and over two-thirds of the births (67.1%; n=487) were attended by traditional birth attendants.

The mean gestational age at birth of the children with CP was 38.2 weeks (SD 3.1 wks). Altogether, 16.3% (n=119) were born preterm (i.e. <37wks). Birthweight was known for only 19.4% of children (n=141; mean 2648.9g). In total, 61.8% children had probable intrapartum-related neonatal respiratory depression, 42.8% had early feeding

Table II: Prevalence of cerebral palsy (CP) by gestational age in children aged ≥5y (n=478)

	BCPR, n (%)	Percentage of live births in a Bangladeshi cohort[31]	Estimated number of live births in Shahjadpur[a] (1998–2011)[21,31]	Prevalence of CP per 1000 live births (95% CI)
Term (≥37wks)	402 (84.1)	80.6	134 672	3.0 (2.7–3.3)
Preterm (28–36wks)	76 (15.9)	19.4	32 415	2.3 (1.9–2.9)
Very preterm (28–31wks)	34 (7.1)	2.6	4344	7.8 (5.6–10.9)
Moderate preterm (32–33wks)	6 (1.3)	3.3	5514	1.1 (0.5–2.4)
Late preterm (34–36wks)	36 (7.5)	13.5	22 557	1.6 (1.2–2.2)

[a]The estimated number of live births in Shahjadpur has been calculated from the percentage of live births reported in a Bangladeshi cohort[31] from the surveillance area of the Bangladesh Population and Housing Census.[21] BCPR, Bangladesh Cerebral Palsy Register; CI, confidence interval.

Table III: Associated impairments in children with cerebral palsy in comparison to national data

Associated impairments[a]	BCPR, n (%)	Bangladesh national data (%)	p
Epilepsy	170 (23.4)	1.2[52]	<0.001
Intellectual	281 (38.7)	0.11[47]	<0.001
Visual	73 (10.1)	0.09[47]	<0.001
Hearing	74 (10.2)	0.05[47]	<0.001
Speech	487 (67.1)	0.18[47]	<0.001

[a]Multiple impairments were reported for several children. BCPR, Bangladesh Cerebral Palsy Register.

difficulty, and 30.9% had possible neonatal encephalopathy. The known maternal and perinatal risk factors are given in Table IV along with a comparison of Bangladesh national data and local data percentages for the general population. Neonatal jaundice was reported in 4.1% (n=30) of the children. Altogether, 15.8% (n=115) of the cohort had a history of consanguinity and 8.3% (n=5) of the children with dyskinesia had history of consanguinity.

The families of the BCPR cohort had a slightly better housing, water, and sanitation status than the general population. However, the proportion of families living below the poverty line was significantly (five times) greater in the BCPR cohort than in the general population in the surveillance area. Moreover, antenatal care was relatively poor in mothers of children in the BCPR cohort compared with the general population; a greater proportion of mothers from the BCPR cohort did not receive any antenatal check-up and delivered their child at home. Furthermore, there were significantly higher levels of preterm births, probable intrapartum-related neonatal respiratory depression, and feeding difficulties among the BCPR cohort compared with the general population.

Access to rehabilitation

The majority (n=568; 78.2%) of the children never received any rehabilitation services. Of these families, 64.8% (n=368) were unaware of the need for rehabilitation, 14.3% (n=81) could not afford the required services, and 4.2% (n=24) could not access the services owing to lack of disability accessible transport.

Only one-fifth (21.8%) of the children had access to rehabilitation services at non-governmental organization centres and/or hospitals. The mean age at which these children first received rehabilitation services was 4 years and 2 months (SD 3y 2.4mo). Among them, 28.5% received physical therapy and of the 495 children in GMFCS level III to V who could have benefited from assistive mobility equipment, only 5.5% (n=27) had any assistive devices.

Those who received rehabilitation had a higher family income (113.6USD vs 100.0USD; p=0.447). Mean age at assessment and mean age at diagnosis of children with CP were significantly different between those who received rehabilitation and those who did not (6y 10.8mo vs 7y 9.6mo [p=0.03] and 4y 2.4mo vs 5y 6mo [p<0.001] respectively). Table SI, online supporting information, shows the differences in sociodemographic, perinatal, and clinical characteristics between the two groups.

Mortality

During the study period, 26 children with CP died (19.8 deaths per 1000 person-years of observation). Mean age at death was 7 years 5 months (SD 5y 2.4mo); 65.4% were male, 34.6% were female. Spasticity was the most common type of CP (n=14 [53.9%]), while the remaining children had dyskinetic (n=3 [11.5%]) or hypotonic (n=9 [34.6%]) CP. Most children who died had severe functional mobility limitations (GMFCS level III–V, n=22 [84.6%]). Almost two-thirds (n=16 [61.5%]) of these children never received any rehabilitation services.

Nutritional status of the deceased children was particularly poor. The mean z-scores for weight for age (calculated for 20/26 children aged 0–121mo), height for age, and weight for height (calculated for 14/26 children aged ≤60mo) were −3.3 (SD 1.4), −4.6 (SD 2.9), and −1.4 (SD 3.4) respectively. In total, 75.0% (n=15) were severely underweight, 76.9% (n=20) were severely stunted, and 50.0% (n=7) had severe acute malnutrition (severe underweight: weight for age less than −3SD, severe stunting: height for age less than −3SD, severe wasting: weight for height less than −3SD). Furthermore, five of the deceased children had both severe acute malnutrition and severe chronic malnutrition.

Table IV: Comparison of demographics and known maternal and perinatal risk factors for cerebral palsy with local and national data for general population

	BCPR, *n* (%)	Local/national data (%)	*p*
Local data			
Area of residence (*n*=726)			
Semi-urban	121 (16.7)	11.5[21]	<0.001
Rural	605 (83.3)	88.5[21]	<0.001
Type of accommodation (*n*=726)			
Temporary shelter (jhupri)	5 (0.7)	2.1[21]	0.002
Mud houses (kutcha house)	591 (81.4)	87.0[21]	<0.001
Semi-pucca house	108 (14.9)	8.3[21]	<0.001
Permanent brick (pucca) house	22 (3.0)	2.6[21]	0.263
Source of drinking water (*n*=726)			
Tap water	6 (0.8)	1.0[21]	0.411
Tube-well	720 (99.2)	95.4[21]	<0.001
Other sources (well, ponds, river)	0	3.6[21]	–
Sanitation (*n*=725)			
No toilet facility	9 (1.2)	2.6[21]	0.009
Non-sanitary latrine	265 (36.5)	51.5[21]	<0.001
Sanitary latrine	451 (62.1)	45.9[21]	<0.001
National data			
Family income			
Families living below poverty line (daily income per capita <1.90USD)	706 (97.2)	18.50[53]	<0.001
Antenatal care (*n*=726)			
No	262 (36.1)	21.4[53]	<0.001
Regular	220 (30.3)	31.2[53]	0.316
Irregular (>2 visits)	142 (19.6)	29.4[53]	<0.001
Irregular (≤2 visits)	102 (14.0)	17.9[53]	0.003
Place of birth (*n*=726)			
Home	528 (72.7)	63.0[53]	<0.001
Health facility	198 (27.3)	37.0[53]	<0.001
Mode of delivery (*n*=726)			
Caesarean section	66 (9.1)	23.0[53]	<0.001
Vaginal birth	660 (90.9)	77.0[53]	<0.001
Delivery attended (*n*=726)			
Doctor/midwife	214 (29.5)	42.1[53]	<0.001
Traditional birth attendant	487 (67.1)	47.6[53]	<0.001
Other family member	25 (3.4)	6.3[53]	<0.001
Gestational age (wks) (*n*=726)			
Term (≥37)	607 (83.6)	80.5[31]	0.018
Very preterm (28–31)	59 (8.1)	2.6[31]	<0.001
Moderate preterm (32–33)	9 (1.2)	3.3[31]	<0.001
Late preterm (34–36)	51 (7.0)	13.5[31]	<0.001
Low birthweight (<2500g)[a] (*n*=141)	53 (37.6)	36.7[54]	0.445
Probable IPR NRD (*n*=607)[b]	380 (62.7)	22.0[55]	<0.001
Early feeding difficulty (*n*=724)	311 (42.9)	10.9[55]	<0.001
Maternal complications during child birth (*n*=726)	344 (47.4)	–	–
Maternal fever during pregnancy (*n*=726)	147 (20.2)	–	–

[a]Birthweight unknown for 585 cases. [b]Probable IPR NRD was defined as neonatal respiratory depression among infants born at term (*n*=607) without congenital malformations. USD, US dollars; IPR NRD, intrapartum-related neonatal respiratory depression.

DISCUSSION

To the best of our knowledge, this is one of the first population-based surveillance studies of children with CP in a LMIC. We adopted an easily replicable and cost-effective model for collection of population-level data, which will serve as a tool for coordination of services for children with CP, and for future research on the epidemiology of CP in LMICs across the world.[20]

Our findings suggest that the burden of CP is high in Bangladesh compared with HICs and other LMICs.[6,13,15,22] However, our reported prevalence is an underestimate owing to delayed diagnosis and strong survival bias.

In our study, the mean age at diagnosis of CP was 5 years and 2 months, which is considerably delayed compared with HICs (e.g. 1y 5mo in Australia).[34] Existing knowledge supports the importance of early diagnosis in ensuring referral to early intervention for optimization of infant motor and cognitive plasticity, prevention of secondary complications, and enhancement of caregivers' well-being.[34] Although systematic reviews of randomized controlled trials identified limited, heterogenous, and weak evidence on the long-term effect of early intervention,[35] several interventions appear promising in yielding a better outcome in children with CP.[36] Less than a fifth of our cohort were diagnosed within the first 1000 days of life;

among them, the majority were diagnosed during the assessment camps as part of this study. Therefore, it is evident that early intervention is largely limited by failure in early diagnosis. Furthermore, owing to delayed diagnosis, it is likely that we have underestimated the number of younger children (i.e. those aged <5y 2mo), resulting in an underestimate of prevalence.

Our findings reflect the high mortality rate in children with CP. We speculate that an additional number of children died before being identified as having CP, particularly considering the delayed diagnosis. Therefore, the observed prevalence is almost certainly affected by survival bias and should be considered an underestimate of the true prevalence in Bangladesh.

Preterm birth, a common cause of CP in HICs, is relatively underrepresented in our study. Moreover, the prevalence of CP was higher in children born at 34 weeks to 36 weeks' gestation, than in those born at 32 weeks to 33 weeks' gestation. This is possibly owing to the high mortality of infants born very preterm in low-resource settings, and there is a strong survival bias at play in low-resource settings such as the study site, where facilities are inadequate for neonatal resuscitation.[37] However, we found that the prevalence of CP is nearly fourfold higher in children born very preterm. Although Bangladesh is among the top-10 countries with the greatest number of preterm births,[38] it has made considerable progress over the past decades.[39] However, successes in neonatal survival are counteracted by concerns of resultant increases in adverse neurodevelopmental outcomes, particularly CP.[40]

Of the known risk factors for CP, we found an alarmingly high proportion of probable intrapartum-related neonatal respiratory depression in children with CP. Many of those children had early feeding difficulty and possible neonatal encephalopathy. Neonatal jaundice was also reported in our cohort. Measures should be taken to address the prevalent risk factors that are potentially modifiable by quality perinatal care.

Associated impairments among children with CP is high and intellectual disability is a common accompanying impairment. We observed a significantly higher prevalence of intellectual impairment among our cohort compared to the national data. UNICEF reported that 'Estimates of the proportion of children with disabilities in Bangladesh are even more varied, ranging from less than 1.4 per cent to 17.5 per cent'.[41] Hence, we speculate that the national data for the prevalence of intellectual impairment is possibly not representative of the true burden. Furthermore, a comparable rate of 45.0% was observed in another population-based study conducted in Australia.[42]

Compared with the Australian CP Register, our cohort had fewer children with hemiplegia and monoplegia (34.3% vs 39.1%) and more severe GMFCS classifications were observed (GMFCS levels III–V: 68.2% vs 40.4%).[15] These reflect a greater need for rehabilitation services and assistive devices among these children.

Our study showed significant differences among children who had received rehabilitation services compared with those who had not. A significantly higher proportion of parents of children who had access to rehabilitation services were literate (49.1% vs 33.1%; $p<0.001$), and the diagnosis of CP in those children was established earlier (mean age at diagnosis 5y 6mo vs 4y 2.4mo; $p<0.001$) but was still late compared with developed countries. This suggests that reports from studies recruiting children from rehabilitation centres or hospitals are not representative of the general population, particularly in LMICs, where most children with CP are deprived of basic health care and rehabilitation services. Owing to the unique method of case ascertainment and population-level surveillance, we believe our study reflects the true picture of CP.

Children with CP and their families are disadvantaged compared with their counterparts in the general population in Bangladesh with significant disparities in basic demographic, antenatal, and perinatal indicators. Disability and poverty perpetuate one another.[43] The majority of our cohort were living below the poverty line. Low socio-economic status was reported to be associated with increased risk of CP in several countries.[44] A population-based study in the USA reported that black infants were 29% more likely to have CP than white infants.[45] The increased risk of CP was found to be primarily related to their higher risk of low birthweight and prematurity, owing largely to suboptimal prenatal care as a consequence of socio-economic factors. Socio-economic deprivation is a risk factor for more severe functional limitations in children with CP.[46] Disability can, in turn, lead to poorer living standards through limited access to education, employment, and health services.[47]

In Bangladesh, special education/schools are limited, with an alarmingly low number of seats (~2000 seats) available for disability inclusive education.[42] Less than half (40.3%) of disabled children receive any education versus 69.7% of typically developing children.[47] Primary and secondary education providers in the study area do not have the facility to support children with special needs and none of them are equipped with trained teachers. Moreover, special education training of teachers is largely lacking in Bangladesh.

Findings from a study conducted in rural settings in a LMIC (i.e. Pakistan) highlight the cardinal role of preventive and promotive maternal and newborn interventions through community health workers.[48] Hence, ensuring equitable access to quality perinatal care through a combination of facility-based and community-based approaches can be a key preventive strategy in countries such as Bangladesh.

Limitations

One of the major challenges in establishing a population-based register is completeness of case ascertainment. The key informant's method has a 77.6% case ascertainment rate compared with a door-to-door survey for identifying children with physical impairments in LMICs when it is

conventionally conducted over a short period.[23,24] It is likely that we have accounted for most of the children with CP alive during the collection of baseline information for the BCPR owing to our ongoing engagement in the surveillance area. However, as diagnosis of CP is delayed, it is likely that complete ascertainment has not been possible in young children (i.e. aged <5y). Furthermore, owing to a high mortality rate in children with CP in LMICs,[48] many children born between 1998 and 2014, especially those with more severe CP, would have died long before the formation of the registry. Hence, our reported prevalence is likely to be an underestimate of the actual burden.

We followed a strict clinical definition of CP adopted from established register networks in Europe and Australia.[15,21] In our setting (i.e. remote and rural) clinical records were limited mainly to hospital discharge summaries, doctors' consultation reports, prescriptions, and immunization cards. Therefore, for some information (including risk factor data), we had to rely predominantly on parental interview. Moreover, estimation of gestational age based on last menstrual period, patient's history, and limited available medical records were the only possible option. Although there is existing evidence that mothers can accurately report the majority of prenatal and perinatal events,[49] and that the last menstrual period provides an accurate estimate of gestational age,[50,51] this information could have been affected by recall bias.

The establishment of a precise diagnosis/description of CP was challenging, particularly for children aged younger than 5 years, as the clinical presentation and CP subtype can change over time. There is also the possibility that some children with mild CP may not have been identified for inclusion.

CONCLUSION

In Bangladesh, a typical LMIC, the burden of CP is high and diagnosis is frequently delayed, resulting in limited opportunities for early intervention during a time of high brain plasticity. Additionally, rehabilitation services are limited and not easily accessible. There are numerous potentially modifiable risk factors for CP in Bangladesh. Therefore, equitable access to quality perinatal care should be prioritized for effective prevention.

SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Bangladesh Cerebral Palsy Register registration form.

Table SI: Comparison of children with cerebral palsy who received rehabilitative services with those who never received any rehabilitation

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RESUMEN

EPIDEMIOLOGÍA DE LA PARÁLISIS CEREBRAL EN BANGLADESH: UN ESTUDIO DE VIGILANCIA BASADO EN LA POBLACIÓN

OBJETIVO Examinar la prevalencia, las características clínicas y los factores de riesgo de la parálisis cerebral (PC) en niños en Bangladesh.

MÉTODO El Registro de PC (BCPR siglas en ingles) de Bangladesh es una base de datos de vigilancia basada en la población de niños con PC, de un área geográficamente definida, en Bangladesh. Los casos se definieron siguiendo los criterios de vigilancia de PC en Europa y los criterios del registro de PC australiano, teniendo en cuenta las evaluaciones clínicas y la identificación por el método del informante clave.

RESULTADOS En total, se identificaron 726 niños con PC entre enero del 2015 y diciembre del 2016. La edad media fue de 7 años y 7 meses (desviación estándar [DE] 4ª 6m; rango: 4,8m-18a; mediana 7a 1,2m; 61,8% masculino, 38,2 % femenino). La edad promedio en el diagnóstico de PC fue de 5 años y 2 meses (DE 3.8). La prevalencia observada fue de 3,4 por cada 1.000 niños (intervalo de confianza [IC] del 95%: 3,2-3,7), resultando en un número estimado de 233.514 niños con PC (IC del 95% 219 778-254 118) en Bangladesh. La mayoría (79.6%) tenía PC espástica. En total, el 79.6% de los niños con PC tenían al menos un impedimento asociado (habla 67.6%, intelectual 39.0%, epilepsia 23.7%, visual 10.2% y audición 10.2%). En total, el 78.2% nunca recibió rehabilitación.

INTERPRETACIÓN En Bangladesh, el impacto de PC es alto y el diagnóstico se retrasa sustancialmente, lo que limita las oportunidades de intervención temprana. Hay una falta de servicios disponibles y la mayoría de los niños tenían factores de riesgo prevenibles.

RESUMO

EPIDEMIOLOGIA DA PARALISIA CEREBRAL EM BANGLADESH: UM ESTUDO DE VIGILÂNCIA COM BASE POPULACIONAL

OBJETIVO Examinar a prevalência, características clínicas, e fatores de risco para paralisia cerebral (PC) em crianças de Bangladesh.

MÉTODO O Registro de PC de Bangladesh (RPCB) é uma base de dados populacional em andamento para vigilância de crianças com PC de uma área geograficamente definida de Bangladesh. Os casos foram definidos com base nos critérios do Vigilância da PC na Europa e do Registro Australiano de PC após avaliação clínica e identificação pelo método pelo informante principal

RESULTADOS No total, 726 crianças com PC foram identificadas entre Janeiro 2015 e Dezembro 2016. A média de idade foi 7 anos e 7 meses (desvio padrão [DP] 4a 6m; variação: 4,8m–18a; mediana 7a 1,2m; 61,8% do sexo masculino, 38,2% do sexo feminino). A média de idade no momento do diagnóstic de PC foi de 5 anos e 2 meses (DP 3,8). A prevalência observada foi 3,4 a cada 1000 crianças (intervalo de confiança [IC] a 95% 3,2–3,7), resultando em uma estimativa de 233.514 crianças (IC 95% 219.778–254.118) com PC em Bangladesh. A maioria (79,6%) tinha PC espástica. No total, 79,6% das crianças com PC tinha pelo menos uma deficiência associada (linguagem 67,6%, intelectual 39,0%, epilepsia 23,7%, visual 10,2%, e auditiva 10,2%). No total, 78,2% nunca recebeu reabilitação.

INTERPRETAÇÃO Em Bangladesh, o peso da PC é alto, e o diagnóstico é substancialmente tardio, limitando as oportunidades de intervenção precoce. Há carência de serviços disponíveis, e a maioria das crianças apresentou fatores de risco preveníveis.

খিঁচুনির চিকিৎসায় ঔষধ ব্যবহারের নির্দেশিকা

সূচীপত্র

খিঁচুনি ব্যবস্থাপনার ঔষধ সমূহঃ

খিঁচুনি ব্যবস্থাপনার ঔষধ সমূহঃ

ফেনোবারবিটোন

- ঔষধের মাত্রা
    - ১ থেকে ৬ মিলিগ্রাম/কেজি হিসেবে প্রতিদিন এক বা দুইবার দেয়া যাবে; ঔষধের সর্বনিম্ন মাত্রা থেকে ব্যবহার শুরু করে প্রয়োজনে ঔষধের মাত্রা ধীরে ধীরে বাড়াতে হবে।

- যে ধরনের খিঁচুনির জন্যে উপকারী
    - সারা শরীর জুড়ে খিঁচুনি এবং শরীরের একাংশের খিঁচুনির জন্যে দেয়া হয়।
    - বারবার শরীরে জ্বরের সাথে সাথে খিঁচুনি হলে দেয়া হয়।
    - জন্মের পর প্রথম ২৮ দিনে বা নবজাতক বয়সে খিঁচুনি হলে (Neonatal Seizure)
    - "অ্যাবসেন্স" খিঁচুনি (Absence Seizure) বা ফাঁকা দৃষ্টিতে চোখ খোলা রেখে যে খিঁচুনি হয় তাতে এই ঔষধ প্রয়োগে কোন উপকার পাওয়া যায়না।

- পার্শ্ব প্রতিক্রিয়া
    - অ্যালার্জি জনিত র্যাশ হতে পারে। হাইপারসেনসিটিভিটি রিঅ্যাকশন হতে পারে, যদিও তা এখন পর্যন্ত খুব কম সংখ্যক রোগীর ক্ষেত্রে দেখা গিয়েছে।
    - অতিক্রিয়াশীল বা শিশু অতি চঞ্চল হতে পারে।
    - তন্দ্রাচ্ছন্নতা বা ঘুম ঘুম ভাব।

- মন্তব্য
    - সাধারনত কোন ভালো ঔষধ নিয়মিত রোগীকে গ্রহন করতে হয় যদি না ঔষধ রোগীর কোন পার্শ্ব প্রতিক্রিয়া না হয় বা রোগ সারিয়ে না তোলে।
    - যদি রোগী এই ঔষধ তিন মাসের বেশি ব্যবহার করে থাকে সেক্ষেত্রে হঠাত করে ঔষধ বন্ধ করে দেয়া যাবেনা। কয়েক সপ্তাহ ধরে ধীরে ধীরে মাত্রা কমিয়ে একসময় ঔষধ পুরোপুরি বন্ধ করতে হবে।

সোডিয়াম ভ্যালপ্রোয়েট

- ঔষধের মাত্রা
  - রোগীর শরীরের প্রতি কেজি ভরে ২০ থেকে ৪০ মিলিগ্রাম হারে হিসেব করে প্রতিদিন দুইভাগে ভাগ করে ঔষধ দিতে হবে। শুরুতে শরীরের প্রতি কেজি ভরে ৫ থেকে ১০ মিলিগ্রাম/দিন হারে শুরু করে প্রতি কেজি ভরে ধীরে ধীরে ২০ মিলিগ্রাম পর্যন্ত ঔষধ বাড়াতে হয়। এরপর প্রয়োজনে মাত্রা বাড়ানো যায়।

- যে ধরনের খিঁচুনির জন্যে উপকারী
  - সকল ধরনের খিঁচুনির জন্যে প্রযোজ্য।

- পার্শ্ব প্রতিক্রিয়া
  - অতিক্রিয়াশীল বা শিশু অতি চঞ্চল হতে পারে।
  - যকৃত বা লিভার এর কার্যক্ষমতা কমে যেতে পারে।
  - দুই বছর বয়সের কম বা বেশি যে সকল শিশু সঠিক ভাবে বেড়ে উঠেনি বা দেরিতে বৃদ্ধিপ্রাপ্ত হয়েছে বা যেসকল শিশুর সত্যি সত্যি সেরেব্রাল পালসি হয়নি তাদের ক্ষেত্রে সোডিয়াম ভ্যালপ্রোয়েট সাবধানে ব্যবহার করতে হবে। শিশুর মাইটোকন্ড্রিয়াল ডিসফাংশন এর ইতিহাস থাকলে ভ্যালপ্রোয়েট যকৃত অকার্যকর করে মৃত্যু ঘটাতে পারে। মাইটোকন্ড্রিয়াল ডিসফাংশন শিশুর ঋণাত্মক প্রবৃদ্ধি বা আগের চাইতে খারাপ শারিরীক অবস্থা দিয়ে বোঝা যায়ঃ যেমন যে শিশু আগে বসতে সক্ষম ছিলো সে এখন বসতে পারেনা, এটিই ঋণাত্মক প্রবৃদ্ধি।

- মন্তব্য
  - যে কোন ধরনের খিঁচুনিতে ভ্যালপ্রোয়েট ভালো কাজ করে এবং ফেনোবারবিটোন এর মতো রোগীর উপর তন্দ্রাচ্ছন্নতার মতো কোন প্রতিক্রিয়া তৈরী করেনা।
  - সোডিয়াম ভ্যালপ্রোয়েট, ক্লোবাজাম এবং ল্যামোট্রিজিন এর সাথেও একসাথে কাজ করতে পারে।
  - চিকিৎসা হিসেবে সোডিয়াম ভ্যালপ্রোয়েট ঔষধ গ্রহন করছে, এমন রোগীর ক্ষেত্রে ল্যামোট্রিজিন খুব সাবধানে ব্যবহার করতে হবে।

ক্লোবাজাম

- ঔষধের মাত্রা
  - শুরুতে ১- ২ মিলিগ্রাম ডোজে দৈনিক একবার প্রয়োগ করতে হবে। এরপর নিম্নবর্নিত উপায়ে ঔষধের মাত্রা বাড়ানো যায়ঃ
    - বয়স ২ বছরের কম হলেঃ ২.৫- ৫ মিলিগ্রাম দৈনিক দুই বেলা,
    - বয়স ২- ১০ বছর হলে ৫- ১০ মিলিগ্রাম দৈনিক দুই বেলা,
    - বয়স ১০ বছরের উর্ধ্বে হলে ১০ মিলিগ্রাম দৈনিক তিনবেলা,
    - মেইন্টেনেন্স এর ক্ষেত্রে ০.৩- ১ মিলিগ্রাম/কেজি/দিন হারে মোট ঔষধ দুই বেলায় ভাগ করে দিতে হবে।
- উপরে বর্নিত ঔষধের মাত্রা হচ্ছে মূল গাইডলাইন, ছোট শিশুদের ক্ষেত্রে এর চাইতে বেশী মাত্রাতেও ঔষধ ব্যবহার করা যায় যদি শিশুর শরীরে কোন পার্শ্বপ্রতিক্রিয়া দেখা না দেয় এবং খিঁচুনি নিয়ন্ত্রনে সহায়ক হয়।

- যে ধরনের খিঁচুনির জন্যে উপকারী
  - সকল ধরনের খিঁচুনির জন্যে প্রযোজ্য,
  - ডিসটোনিয়া ব্যবস্থাপনার ক্ষেত্রেও কিছু কিছু ক্ষেত্রে এই ঔষধ কাজ করে।

- পার্শ্ব প্রতিক্রিয়া
  - তন্দ্রাচ্ছন্নতা,
  - অতিক্রিয়াশীল বা শিশু অতি চঞ্চল হতে পারে।
  - হ্যালুসিনেশন।
  - মুখ থেকে ক্রমাগত লালা ঝরতে পারে।
- মন্তব্য
  - মনোথেরাপি হিসেবে কার্যকর এবং খিঁচুনির অন্য ঔষধের সাথেও ব্যবহার উপযোগী।
  - স্বল্পমাত্রার ডোজ যেমন ১ মিলিগ্রাম দৈনিক দুইবার হারে ব্যবহার শুরু করে মাত্রা বাড়ানো যায়।
  - স্বল্পমাত্রায় পাওয়া না গেলে ঔষধ গুড়ো করে পানির সাথে মিশিয়ে স্বল্পমাত্রায় খাওয়ানো যায়।
  - অভিভাবক যদি পানিতে গুলিয়ে খাওয়ানোর মাত্রা না বোঝেন, সেক্ষেত্রে ট্যাবলেটের চারভাগের একভাগ বা অর্ধেক করেও রোগীকে খাওয়ানো যায়।
  - কোন কোন ক্ষেত্রে শিশুদের শরীর বেনজোডায়াজেপিন এ অভ্যস্ত হয়ে পরে। যদি বেশ কয়েকমাস খিঁচুনির সম্পূর্ন নিয়ন্ত্রনের পর হঠাত আবার দেখা দেয়, সেক্ষেত্রে অন্য বেনজোডায়াজেপিন যেমন নাইট্রাজেপাম চিকিৎসায় ব্যবহার করতে হয়।

নাইট্রাজেপাম

- ঔষধের মাত্রা
  - ১ মাস থেকে ২ বছর বয়সের মাঝে এই ঔষধ শুরু করতে হবেঃ শরীরের প্রতি কেজি ভরে ০.২৫ মিলিগ্রাম হারে দৈনিক দুইবার থেকে শুরু করে, প্রতি কেজি ভরে ০.৫ মিলিগ্রাম হারে দৈনিক দুইবার দেয়া যায়।
  - উপরে বর্নিত ঔষধের মাত্রা হচ্ছে মূল গাইডলাইন, ছোট শিশুদের ক্ষেত্রে এর চাইতে বেশী মাত্রাতেও ঔষধ ব্যবহার করা যায় যদি শিশুর শরীরে কোন পার্শ্বপ্রতিক্রিয়া দেখা না দেয় এবং খিঁচুনি নিয়ন্ত্রনে উপকারী হয়।

- যে ধরনের খিঁচুনির জন্যে উপকারী
  - সকল ধরনের খিঁচুনির জন্যে প্রযোজ্য,
  - ইনফ্যান্টাইল স্পাজম (Infantile Spasm) এর ক্ষেত্রেও প্রযোজ্য।

- পার্শ্ব প্রতিক্রিয়া
  - তন্দ্রাচ্ছন্নতা,
  - মুখ থেকে ক্রমাগত লালা ঝরতে পারে।

- মন্তব্য
  - মনোথেরাপি হিসেবে কার্যকর এবং খিঁচুনির অন্য ঔষধের সাথেও ব্যবহার উপযোগী।
  - স্বল্পমাত্রার ডোজ থেকে ব্যবহার শুরু করে এর মাত্রা বাড়ানো যায়।
  - যদি রোগী খিঁচুনির চিকিৎসায় তিন মাসের বেশি নাইট্রাজেপাম পেয়ে থাকে এবং ঔষধ বন্ধ করার প্রয়োজন হয়, সেক্ষেত্রে ফেনোবারবিটোন এর মতো ধীরে ধীরে মাত্রা কমিয়ে কমিয়ে বন্ধ করতে হয়।
  - কোন কোন ক্ষেত্রে শিশুদের শরীর বেনজোডায়াজেপিন এ অভ্যস্ত হয়ে পরে। যদি বেশ কয়েকমাস খিঁচুনির পুরোপুরি নিয়ন্ত্রনের পর আবার হঠাত দেখা দেয়, সেক্ষেত্রে অন্য বেনজোডায়াজেপিন যেমন ক্লোবাজাম চিকিৎসায় ব্যবহার করতে হয়।

কার্বামাজেপাইন

- ঔষধের মাত্রা
  - শরীরের প্রতি কেজি ভরে ১০- ২০ মিলিগ্রাম হারে হিসেব করে যতোটুকু ঔষধ হয় তা ২৪ ঘন্টায় ২ বা ৩ ভাগে ভাগ করে ডোজ হিসেবে দিতে হয়; শুরুতে শরীরের প্রতি কেজি ভরে ২.৫- ৫ মিলিগ্রাম প্রতিদিন হারে দেয়া শুরু করে পরবর্তীতে ধীরে ধীরে শরীরের প্রতি কেজি ভরে দৈনিক ১০ মিলিগ্রাম পর্যন্ত বাড়ানো যায় দিনে ২ বা ৩ ভাগে দিতে হয়। এরপর ঔষধের মাত্রা প্রয়োজন অনুযায়ী বাড়ানো যায়। কোন কোন রোগী স্বল্প মাত্রায় যেমন ৫- ১০ মিলিগ্রাম/কেজি/দিন হারেই সুস্থ থাকে; সেক্ষেত্রে পরবর্তী প্রয়োজন ছাড়া ঔষধের একই মাত্রা বজায় রাখতে হয়।

- যে ধরনের খিঁচুনির জন্যে উপকারী
  - শরীরের একাংশ বা কোন বিশেষ অংশের খিঁচুনির (Focal Seizure) জন্যে প্রযোজ্য।
  - সারা শরীরের খিঁচুনি বা অ্যাবসেন্স সিজার (Absence Seizure) এবং ফেব্রাইল সিজার (Febrile Seizure) এর জন্যে এই ঔষধ উপযোগী নয়।

- পার্শ্ব প্রতিক্রিয়া
  - শিশু অতিক্রিয়াশীল বা অতি চঞ্চল হতে পারে,
  - যকৃত বা লিভারের কার্যক্ষমতা লোপ পেতে পারে বা কমে যেতে পারে।
- মন্তব্য
  - শরীরের একাংশ বা কোন বিশেষ অংশের খিঁচুনির জন্যে উপকারী ঔষধ, যেমন হেমিপ্লেজিক সেরেব্রাল পালসির সাথে থাকা খিঁচুনি।

ডিসটোনিয়া/স্পাসটিসিটি ব্যবস্থাপনার ঔষধ সমূহঃ

ট্রাইহেক্সিফেনিডিল/বেনজহেক্সোল

- ঔষধের মাত্রা
  - ০.২৫ মিলিগ্রাম ২৪ ঘন্টায় একবার থেকে শুরু করে ধীরে ধীরে একই মাত্রার ঔষধ (০.২৫ মিলিগ্রাম) ২৪ ঘন্টায় তিনবার পর্যন্ত ব্যবহার করা যায়।
  - ঔষধ শরীরে সহনীয় হলে ২৪ ঘন্টায় ২- ৪ মিলিগ্রাম হারে তিনবার পর্যন্ত বাড়ানো যেতে পারে।
  - বয়স্ক বাচ্চাদের ক্ষেত্রে উপকার পেলে উচ্চমাত্রায় এই ঔষধ দেয়া যায়।
- যে ধরনের লক্ষনের ক্ষেত্রে উপকারী
  - মূলত ডিসটোনিয়া বা যেসকল সেরেব্রাল পালসিতে নিস্তেজ পেশী দেখা যায় তার ব্যবস্থাপনায় এই ঔষধ ব্যবহার হয়। এতে করে অনেক ক্ষেত্রে বাচ্চার লালা ঝরার প্রবনতাও কমে যায়। কারন এই ঔষধের অ্যান্টিকোলেনার্জিক বৈশিষ্ট্য রয়েছে।
- পার্শ্ব প্রতিক্রিয়া
  - মুখ ও চোখ শুষ্ক হতে পারে,
  - কোষ্ঠকাঠিন্য,
  - দ্বিধান্বিত চিন্তাভাবনা,
  - একই জিনিষ দুটো করে দেখা,
  - রোগীর খিটখিটে মেজাজ দেখা যেতে পারে।
- মন্তব্য
  - পার্শ্বপ্রতিক্রিয়া কোন সমস্যা তৈরী না করলে ডিসটোনিয়া ব্যবস্থাপনার ক্ষেত্রে এই ঔষধের দক্ষতা প্রায় ২৫- ৩০%। কোন কোন শিশুর ক্ষেত্রে এই ঔষধের কর্মক্ষমতা এর চাইতেও বেশি দেখা যায়।
  - এই ঔষধের সাথে অন্য কোন অ্যান্টিকোলেনার্জিক (Anticholenergic) ঔষধ ব্যবহার করা যাবেনা এবং যদি ব্যবহারের পর কোন পার্শ্বপ্রতিক্রিয়া ক্লিনিকাল সমস্যা হিসেবে দেখা দেয় তাহলেও এই ঔষধ ব্যবহার বাদ দিতে হবে।
  - সর্বোচ্চ মাত্রায় ৩- ৪ সপ্তাহ ব্যবহারের পরেও কোন উপকার পাওয়া না গেলে ঔষধ বন্ধ করতে হবে, কারন এই ঔষধ দেরীতে কাজ করেনা।

বেক্লোফেন

- ঔষধের মাত্রা
  - ২- ৭ বছরঃ ১০- ৪০ মিলিগ্রাম প্রতিদিন তিন থেকে চার ভাগে ভাগ করে দেয়া হয়। প্রথমে ২.৫- ৫ মিলিগ্রাম দিনে দুইবার থেকে শুরু করে প্রতি তিন/চার দিনে ৫- ১৫ মিলিগ্রাম পর্যন্ত দেয়া যায়। সর্বোচ্চ ৪০ মিলিগ্রাম প্রতিদিন মাপে ঔষধ দেয়া যায়।
  - ৮- ১১ বছরঃ ১০- ৬০ মিলিগ্রাম প্রতিদিন তিন থেকে চার ভাগে ভাগ করে দেয়া হয়। প্রথমে ২.৫- ৫ মিলিগ্রাম দিনে দুইবার থেকে শুরু করে প্রতি তিন/চার দিনে ৫- ১৫ মিলিগ্রাম পর্যন্ত দেয়া যায়। সর্বোচ্চ ৬০ মিলিগ্রাম প্রতিদিন মাপে ঔষধ দেয়া যায়।
  - ১২ বছর বা তদুর্ধ্বঃ ২০- ৮০ মিলিগ্রাম প্রতিদিন তিন থেকে চার ভাগে ভাগ করে মুখে খেতে দেয়া যায়। প্রথমে ২.৫- ৫ মিলিগ্রাম দিনে দুইবার থেকে শুরু করে প্রতি তিন/চার দিনে ১৫ মিলিগ্রাম পর্যন্ত দেয়া যায়। সর্বোচ্চ ৮০ মিলিগ্রাম প্রতিদিন মাপে ঔষধ দেয়া যায়।
- যে ধরনের লক্ষনের ক্ষেত্রে উপকারী
  - মূলত পেশীর অনৈচ্ছিক শক্ত হওয়া বা স্পাসটিসিটির চিকিৎসায় ব্যবহৃত হয়।
- পার্শ্ব প্রতিক্রিয়া
  - রোগীর হাইপোটোনিয়া বা নিজীব মাংসপেশী তৈরী করতে পারে।
  - রোগীর অনবরত লালা ঝরতে পারে।
  - তন্দ্রাচ্ছন্নতা।
- মন্তব্য
  - স্পাসটিসিটির কারনে শক্ত মাংসপেশির চিকিৎসায় বেক্লোফেন একটি ভালো ঔষধ।
  - মাংসপেশীর নিজীবতা বা ডিসটোনিয়া বেশি থাকলে বা মিশ্র ধরনের ডিসটোনিয়া থাকলে এই ঔষধ ব্যবহার না করাই উত্তম।
  - কিছু কিছু রোগীর ক্ষেত্রে উচ্চ মাত্রায় বেক্লোফেন দেয়া হয়, সেক্ষেত্রে খিটখিটে মেজাজ এর মতো পার্শ্ব প্রতিক্রিয়া হতে পারে। তখন ঔষধের মাত্রা ঠিক করে দিতে হয়।
  - বেনজোডায়াজেপিন বা ফেনোবারবিটোন এর মতো ঔষধ বেক্লোফেন এর সাথে দেয়া হলে রোগীর তন্দ্রাচ্ছন্নতা ও লালা ঝরার মাত্রা বৃদ্ধি পেতে পারে।
  - রোগী তিন মাসের বেশি বেক্লোফেন ব্যবহার করে থাকলে কয়েক সপ্তাহ জুড়ে ধীরে ধীরে ঔষধের মাত্রা কমিয়ে এক সময় তা বন্ধ করতে হবে।

লেভাডোপা/কার্বিডোপা

- ঔষধের মাত্রা
  - শরীরের প্রতি কেজি ভরে ১- ৪ মিলিগ্রাম হারে যে পরিমান ঔষধ হয় তা দুই ভাগে ভাগ করে প্রতিদিন দিতে হয়। শুরুতে প্রতি কেজি ভরে ১ মিলিগ্রাম হারে মোট ঔষধের পরিমান কে দুই ভাগে ভাগ করে ২৪ ঘন্টায় দিতে হবে। ঔষধের মাত্রার পরিমান ধীরে ধীরে বাড়িয়ে শরীরের প্রতি কেজি ভরে ৪ মিলিগ্রাম হারে মোট ঔষধকে ২৪ ঘন্টায় তিন ভাগে ভাগ করে তিন বেলা দিতে হবে।
  - খিঁচুনি স্থানিক বা শরীরে আংশিক স্থানে হলে এবং ঔষধ প্রয়োগে উপকার পেলে ঔষধের মাত্রা বাড়ানো যায়।
- যে ধরনের লক্ষনের ক্ষেত্রে উপকারী
  - ডিসটোনিয়া ব্যবস্থাপনার ক্ষেত্রে।
  - ডিসটোনিয়া বা মাংশপেশীর নিজীবতা যদি স্বাভাবিকভাবেই দিনদিন খারাপের দিকে যায় বা কোন ব্যায়ামের কারনে অবস্থা খারাপ হতে থাকে, সেক্ষেত্রে এই ঔষধ বেশ কাজে দেয়।
- বিরূপ প্রতিক্রিয়া
  - বমি বমি ভাব।

- মন্তব্য
  - সেরেব্রাল পালসির ডিসটোনিয়া ব্যবস্থাপনায় এর সাফল্য শতকরা মাত্র ২৫ ভাগ কিন্তু এই ঔষধ ব্যবহার নিরাপদ।
  - জেনেটিক ডোপামিন রেসপনসিভ ডিসটোনিয়া অনেক সময় সেরেব্রাল পালসি রোগের মতো লক্ষন প্রকাশ করে। এক্ষেত্রে এই ঔষধ বেশ কার্যকর। যদিও এরকম রোগী বেশ কম।
  - এই ঔষধের কিছু কিছু প্রিপারেশান লেভাডোপা/বেনসেরাজাইড হিসেবে পাওয়া যায়। এক্ষেত্রেও ঔষধের পরিমাত্রা লেভোডোপার মতোই হবে।

শিশুর অস্বাভাবিক আচরন ব্যবস্থাপনার ঔষধ সমূহঃ

ক্লোনিডিন

- ঔষধের মাত্রা
    - রাতের ঘুম ঠিক রাখার জন্যে ২৫ মাইক্রোগ্রাম করে রাতে শোবার সময় খেতে দিতে হবে।
    - ২৪ ঘন্টায় তিনবার ২৫ থেকে ১০০ মাইক্রোগ্রাম পর্যন্ত ঔষধের পরিমান বাড়িয়ে আচরন ব্যবস্থাপনার ক্ষেত্রে ব্যবহার করা হয়।

- যে ধরনের উপসর্গ দেখা গেলে শুরু করতে হবে
    - অতিক্রিয়াশীল, চঞ্চল বা অস্থির শিশু বা আক্রমনাত্মক আচরন, যেমনঃ কাউকে কামড়ানো, বিদ্যালয়ে পড়ায় অমনোযোগী হওয়া, বিদ্যালয়ে অন্য শিশুকে বিরক্ত করা, এক জায়গায় স্থির হয়ে বসে না থাকতে পারা (এই লক্ষনগুলোই মূলত বাড়িতে বা বিদ্যালয়ে চঞ্চলতা, অস্থিরতা বা আক্রমনাত্মক আচরন হিসেবে ধরা হয় এবং চিকিৎসার ব্যবস্থা করতে হয়।)
    - মারাত্মক ডিসটোনিয়াতে আক্রান্ত যেসকল রোগী কিছুদিন পরপর অস্বাভাবিক আচরন করে এবং দিন দিন আচরন বেশী খারাপের দিকে যায় তাদের ক্ষেত্রেও এই ঔষধ বেশ কার্যকর। তিন বা চারদিনের জন্যে ২৪ ঘন্টায় ৪ থেকে ৬ বার ১০০ মাইক্রোগ্রাম মাত্রার ঔষধ শর্ট বার্ষ্ট (Short Burst) এর ক্ষেত্রে উপকারী। এরপর আবার ধীরে ধীরে মাত্রা কমিয়ে স্বাভাবিক মাত্রায় নামিয়ে নিয়ে আসতে হয়।
- পার্শ্ব প্রতিক্রিয়া
    - তন্দ্রাচ্ছন্নতা
    - শারীরিক ভঙ্গিগত নিম্ন রক্তচাপ এর কারনে কখনো কখনো তন্দ্রাচ্ছন্নতা দেখা দিতে পারে- বেশি দেখা দেয় সাধারনত ঔষধের নিম্নমাত্রার ক্ষেত্রে।
- মন্তব্য
    - তিন মাসের বেশী ক্লোনিডিন গ্রহন করলে সপ্তাহখানেক সময় নিয়ে ঔষধের মাত্রা কমিয়ে কমিয়ে ঔষধ বন্ধ করতে হয়।
    - মনোযোগে অক্ষমতার রোগীর চিকিৎসার ক্ষেত্রে ক্লোনিডিন এর সাফল্য গড়পড়তা।

রিসপেরিডন

- ঔষধের মাত্রা
  - শিশুদের ক্ষেত্রে দৈনিক ০.২৫ মিলিগ্রাম থেকে শুরু করে সর্বোচ্চ ৫ মিলিগ্রাম পর্যন্ত। সর্বনিম্ন কত মাত্রার ওউষধে কাজ করে তা ভালো করে দেখতে হবে।
- যে ধরনের উপসর্গে ব্যবহার উপযোগী
  - অতি চঞ্চল বা অতি ক্রিয়াশীল বা আক্রমনাত্মক আচরনের রোগীদের ব্যবস্থাপনায় এই ঔষধ ব্যবহার হয়।
- পার্শ্ব প্রতিক্রিয়া
  - ক্ষুধা বৃদ্ধি,
  - শরীরের ভর বৃদ্ধি,
  - বিপাক ক্রিয়ায় গোলমাল- এই ঔষধ লম্বা সময় ধরে ব্যবহার করলে হাইপারলিপিডিমিয়া দেখা দিতে পারে,
  - শরীর শক্ত হয়ে যেতে পারে।
- মন্তব্য
  - ক্লোনিডিন দিয়ে চিকিৎসা শুরু করতে হবে।
  - যেসকল বাচ্চাদের আচরনের কারনে পারিবারিক দৈনন্দিন জীবন ক্ষতিগ্রস্থ, তাদের চিকিৎসায় এই ঔষধ খুবই কার্যকর।

জরুরী অবস্থায় রোগী ব্যাবস্থাপনার ঔষধ সমূহঃ

ডায়াজিপাম

- ঔষধের মাত্রা
  - ৬ বছর বয়সের কম হলে শরীরের প্রতি কেজি ভরে ০.৫ মিলিগ্রাম করে; ৬ থেকে ১১ বছর বয়সের হলে শরীরের প্রতি কেজি ভরে ০.৩ মিলিগ্রাম করে; ১১ বছর বয়সের বেশী হলে শরীরের প্রতি কেজি ভরে ০.২ মিলিগ্রাম হিসেবে দিতে হবে।
- যে ধরনের উপসর্গে ব্যবহার উপযোগী
  - প্রলম্বিত খিঁচুনির ক্ষেত্রে(বাড়িতে ৫ মিনিটের অধিক সময় খিঁচুনি থাকলে)।
- পার্শ্ব প্রতিক্রিয়া
  - ঘুম,
  - শ্বাস গ্রহনে অক্ষমতা এবং মারাত্মক ক্ষেত্রে ফুসফুস এর কাজ বন্ধ হয়ে যাওয়া,
  - লোকাল ইনজুরি।
- মন্তব্য
  - খিঁচুনি আক্রান্ত রোগীর পরিবার ডায়াজিপাম ব্যবহারের প্রক্রিয়া সম্পর্কে পুরোপুরি জানলে বাড়িতে ব্যবহারের জন্যে ব্যবস্থাপত্রে ডায়াজিপাম দেয়া হয়।
  - খিঁচুনির সময় যদি খুব হাত পা নড়ে বা শিশু যদি অজ্ঞান হয়ে যায়, সেক্ষেত্রে প্রাথমিক চিকিৎসার একদম প্রথম ধাপগুলো আগে অনুসরন করতে হয়, যেমনঃ বাইরের যেকোন আঘাত থেকে শিশুকে বাঁচাতে হবে, শ্বাস নেয়ার সুবিধার্থে পাশ করে শুইয়ে দিতে হবে।
  - যা যা প্রয়োজনঃ
    - নরমাল স্যালাইনে মেশানো ডায়াজিপাম ২৫ মিলিলিটার এর বোতলে থাকতে হবে যার এক মিলিলিটার তরলে ১ মিলিগ্রাম ডায়াজিপাম মিশ্রিত থাকবে (ঘনত্বের মাত্রা ভিন্ন ও হতে পারে),
    - পূর্নব্যবহার যোগ্য ১০ মিলিলিটার এর সিরিঞ্জ,
    - সিরিঞ্জের সাথে একটি পূর্নব্যবহারযোগ্য নরম প্লাস্টিক টিউব লাগানো থাকতে হবে যেনো বোতল থেকে ডায়াজিপাম তুলে তা ইনজেক্ট করা যায়,
    - এক স্যাচেট লুব্রিকেন্ট জেলি।

তথ্যসূত্রঃ

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