OPEN ACCESS Freely available online

Journal of Current Synthetic and Systems Biology

Mini-review

Excessive Crying in Children with Cerebral Palsy

Nagabhushana Rao Potharaju*

Department of Consultant Pediatric Neurology, Sathbhavana Brain Clinic, Secunderabad, Telangana, India

ABSTRACT

Pain/discomfort is both under-suspected and underdiagnosed cause of Excessive Crying in Children with Cerebral Palsy and Communication Deficits. It has not been investigated for many decades because of the lack of understanding of the etiology, pathogenesis, pharmacology/pharmacokinetics of drugs, and ethics of the study in pediatric participants who cannot consent to the study. This is the first study to clinically and statistically design and prove a simple and practical algorithm for the management of a challenging task. Diagnosing and treating nociceptive pain at the earliest is imperative, because untreated, under-treated, or mistreated acute pain may lead to chronic pain states confounding treatment. Additionally, a vicious cycle of spasms-pain-spasms sets in as pain continues. In the long run, if the pain is not controlled, the quality of life of children with cerebral palsy and their families worsens. Managing pain in children would reduce the prevalence of chronic pain when they grow up. The drugs and their sequence of usage are decided by the subtype of CP, assumed etiology, the pathophysiology of pain/discomfort, clinical symptoms/signs, accompanying problems, electroencephalography, Magnetic Resonance Imaging (MRI), mechanism of action of the drug, side effects of the drug, and allergies. Treatment of dystonia, spasticity, neuropathic and visceral, pain reduced crying. The drug requirement was reduced after 250 days of treatment with the resolution of the vicious cycle of spasms-pain-spasms. Parents/caregivers reported simultaneous improvement in dysphagia/drool without any additional treatment.

Keywords: Allodynia; Childhood-onset dystonia; Drooling; Dysphagia; Hyperalgesia; Rigidity; muscle spasticity; Neuropathic pain

INTRODUCTION

An excessively crying child with cerebral palsy, worried parents, helpless grandparents, a treating doctor struggling to make an evidence-based diagnosis and treatment, inquisitive caretakers of other patients (trying to assess the efficiency of the doctor by the way he/she manages the crying child) is not a rare scene in pediatric clinics. Diagnosing the cause of Excessive Crying in Children with Cerebral Palsy particularly those with Communication Deficits (ECCCPCD), due to immaturity of the nervous system or global developmental delay, or profound intellectual retardation, is always a challenge. Unless evidence-based management of crying in these children is available, the treatment becomes a trial & error or hit or miss or not offered at all for fear of litigations and referred to various specialists. Referral to those specialists with the resultant delay in the diagnosis and appropriate management hurts the quality of life of both the child and his/her family. Information about the likely etiology and the availability of treatment reduces a parent's anxiety.

LITERATURE REVIEW

Non-progressive refers to the brain's damage only and not the symptoms and signs that change with myelination of various neural pathways and neural plasticity [1] resulting in repair and recovery. Neural adaptability involves either a rapid process that occurs in minutes to hours after denervation, where in "sleeping" inactive synapses or nerve pathways are activated, or a slower process of collateral sprouting and forming new nerve connections [2]. Neuropathic pain is due to "unsuccessful" cortical plasticity [2]. The appearance of hypertonia, exaggerated

Correspondence to: Nagabhushana Rao Potharaju, Department of Pediatric Neurology, Sathbhavana Brain Clinic, Secunderabad, Telangana, India, E-mail: nagabhushanarao@gmail.com

Received: 16-Sep-2022, Manuscript No. CSSB-22-19647; **Editor assigned:** 19-Sep-2022, PreQC No. CSSB-22-19647 (PQ); **Reviewed:** 03-Oct-2022, QC No. CSSB-22-19647; **Revised:** 10-Oct-2022, Manuscript No. CSSB-22-19647 (R); **Published:** 17-Oct-2022, DOI:10.35248/2332-0737.22.10.010.

Citation: Potharaju NR (2022) Excessive crying in children with cerebral palsy. J Curr Synth Syst Bio.10:10

deep tendon reflexes, abnormal posture, and ataxia take months/years [3] to appear because of the time taken for plastic changes and myelination. Pain or discomfort originating from the nervous system was thought to be responsible for excessive crying. [4-7]. Among children with CP, 3 in 4 (75%) are in pain [8]. A lesion anywhere along the neuroaxis responsible for transmitting and regulating pain correlates with the development of Central Post Stroke Pain. [9] Hypersensitivity and hyperalgesia may result from the interaction of the sensory and emotional aspects of pain. Sleep disorders may be associated with pain. [4,10,11].

Spasticity and the other forms of Upper Motor Neuron Syndrome can be very painful (like flexor and extensor spasms). Noxious stimuli, as well as non-noxious stimuli (like yawning, and transferring {allodynia}), can exacerbate spasticity. Pain and sensory phenomena are not rare in dystonia. Pain may occur from over activity of affected muscles or may occur in muscles activated to compensate for dystonia. Occasionally treatment is needed only for analgesia rather than enhancement of function [3]. Pain [12-14], as a cause of excessive crying, in infants and children has been overlooked in research [14]. Acute pain is a biological signal that draws awareness to an area of injury and enforces the rest of the injured part to allow healing [15]. Diagnosing and managing nociceptive pain [16] at the earliest is imperative, because untreated, under-treated [6], or mistreated acute pain may lead to chronic pain states [1,12] confounding treatment. For early diagnosis and intervention, routine screening for pain is important. [5] Additionally, a vicious cycle of spasm-pain-spasm sets in as pain continues. In the long run, if the pain is not controlled, the quality of life of children with cerebral palsy and their families worsens. Managing acute pain in children would reduce the prevalence of chronic pain when they grow up. Invasive procedures are not useful [17] because neurosurgical interruption of a single neural pathway may not alleviate pain. After all, several neural pathways carry pain sensations. So, medical treatment is the option.

DISCUSSION

The development of a simple but reliable algorithm for the management of such cases with proof of clinical and statistical significance is a challenging task and has not even been attempted for many decades. Even when the clinician makes an educated guess about the probable etiology and management, legal accountability frequently deters the doctor from instituting empirical treatment.

Empirical treatment has to be confirmed by statistically valid studies. The trial period has to be long because some drugs take many weeks (clonazepam, tetrabenazine, gabapentin, lamotrigine, and amitriptyline) or months to reach peak effect (e.g., baclofen-2 months and trihexyphenidyl-9 months) and breaking an established vicious cycle of spasm-pain-spasm also takes many months to permit reduction of the dosages. The biggest challenge in conducting any such study is the selection of the study design. Randomized clinical trials or Randomized Control Trials (RCT) are the gold standards of study design since randomization eliminates confounding and minimizes selection bias. Conducting trials lasting more than a year using designs like randomized case-control or stepped wedge design or 2-sequence crossover or starting subjects on active therapy and performing randomized withdrawal would be unethical. Empirical reports, viewpoint articles, and observational studies are inferior to RCT studies. So, a fixed-sequence, crossover clinical trial, is the best ethical design [3]. Making ethical choices, between one good and another good (not between good and bad), in the best interest of the pediatric participant to guard them against long-term consequences of decisions that they did not take, is a difficult one [18]. So, the drugs used in any such study have to be already in use in pediatrics for decades. Only oral medication has to be used so that follow-up treatment at home is possible to reduce the cost of treatment.

The open-access article, "Excessive crying in children with cerebral palsy and communication deficits, a fixed-sequence, crossover clinical trial" (ECCCPCD) [3], is the first and the only dedicated study so far to find a solution to this complicated problem using the available evidence with some unavoidable empirical approach in an ethical study design. This study hypothesized that the pain or discomfort was due to spasticity, dystonia, visceral hyperalgesia, neuropathy, or central pain alone or in combination. This was a fixed-sequence crossover study of 131 consecutive subjects under the age of 15 years with more than 7.5 hours of crying duration per day for 30 straight days. 'Placebo Run-In Period' (PRIP) was used for various reasons for avoiding drop-outs and missing data etc. Interpretation of results from a trial with a PRIP is a challenging task. There is a possibility that PRIP might have affected external validity (by excluding participants from the study population) and internal validity (by the risk of unblinding or amplifying the intention-to-treat effect estimation). It could have affected both economic & logistical costs and the risk of bias. By excluding placebo responders or non-compliers, the run-in period might have augmented the study's power. Full details of all excluded participants before and during the run-in and study periods are presented for judging the risk of compromised validity. Since most of the participants excluded were improbable to be CP, the results were unlikely to be altered significantly. Minimum cry intensity for recording by the caregiver at home was defined in a simple way. The cry duration was recorded if the intensity of crying could mask a radio, TV, or the voice of a person talking to her. It discussed the pathophysiology behind the diagnostic clinical findings, the reasons for the drug selection, and their sequence. Depending on the predominant subtype of CP, assumed etiology & pathophysiology of pain/discomfort, clinical findings, associated problems, Electro Encephalo Graphy (EEG), Magnetic Resonance Imaging (MRI), mechanism of action of the drug, side effects of the drug, and allergies, an empirical drug treatment algorithm was developed for the study [3]. The highlights of the article summarizing the entire available information and the additional information from the dedicated study. Plasticity [2] and maturation of the nervous system confuse drawing evidence-based conclusions in any study lasting 400 days [3]. This along with various weaknesses of a fixed sequence cross-over study were addressed.

The limitations of the study were discussed in depth [3]. The effect of heterogeneity in enrolled participants because of the long study period of >14 years, medication selection, and the

sequence being partly empiric have been minimized by strict inclusion and exclusion criteria. A period effect of plasticity or maturation of inhibitory pathways reducing ECCCPCD has been excluded by the study design. The period effect was excluded by the inclusion of only cerebral palsy cases and the ability to reduce the dose between T251-T310 in 67/131 (51.15%) participants. Like all pain surveys among nonverbal or communicatively impaired participants, the ECCCPCD was dependent on caregivers' proxy reports [19]. Though limitations of research design are inevitable in such studies proved that proxies' reports of total and unexplained crying are observed to be as good as self-reports. Intention to treat analysis was not done because one participant's data would not have significantly changed the result of analyses of one hundred and thirty-one participants. The risk of an ascertainment bias operating was discussed because the study sample was based on consecutive enrollment and not on a random sampling of the ECCCPCD population. It was clarified that the interpretations are specific to the study sample and may not necessarily be illustrative of all children with CP. Moreover, the small number of children studied at one site also limits the generalizability of the conclusions. The diagnosis of allodynia suggesting neuropathic pain, (central or peripheral) is made simple by highlighting observations like ECCCPCD on touching or covering the participant with a bed cloth [20-22].

CONCLUSION

The provision of a simple algorithm based on clinical findings and ubiquitously available investigations is the highlight of the study. The drugs and their sequence of usage are guided by the predominant subtype of CP, assumed etiology, the pathophysiology of pain/discomfort, clinical symptoms/signs, accompanying problems, Electroencephalogram (EEG), Magnetic Resonance Imaging (MRI), mechanism of action of the drug, side effects of the drug, and allergies. For preterm babies, participants with spasticity, or MRI showing periventricular leukomalacia, baclofen/ benzodiazepines are useful, and for dystonia, baclofen/benzodiazepines/ trihexyphenidyl/tetrabenazine are useful in that sequence. The antiepileptic of choice must be added for any associated seizures. When there is no clinical hint to guide drug selection, or MRI shows damage to the putamen, insula, perisylvian area, thalami, basal ganglia, or parietal lobe, “gabapentin, ”topiramate,” “lamotrigine,” “amitriptyline” are useful in that order because visceral hyperalgesia/neuropathic pain is the most likely cause. They probably alleviate pain/discomfort resulting in the reduction of ECCCPCD. The drug requirement was less after 250 days of treatment indicating the resolution of the vicious cycle of spams-pain-spasms.

An interesting observation in the study was the response of dysphagia and drooling in a few cases to the same treatment. Baclofen relaxes the cricopharyngeal muscle and relieves dysphagia. It also decreases the number, frequency & duration of attacks on the lower esophageal sphincter's transient relaxation thus reducing gastroesophageal reflux episodes. Some participants with dysphagia, feeding problems, and drooling responded to trihexyphenidyl/tetrabenazine suggesting that the cause was drool resulting from dysphagia, excessive secretions, or lack of lip control. The anxiolytic effect of drugs used in improving sleep and at least partly reducing ECCCPCD is a possibility. ECCCPCD due to unknown causes is less frequent than that due to known causes. ECCCPCD must be suspected when GMFCS levels are IV and V. The quality of life of the participant, his caregiver, and the family improves when ECCCPCD is controlled. ECCCPCD in progressive encephalopathies may also be managed as per this algorithm because the pathophysiology of crying is probably the same. Cry intensity was defined for one study for statistical purposes. The same drugs and sequence may be used for even lesser cry intensities/durations.

REFERENCES

1. Kuner R, Flor H. Structural plasticity and reorganization in chronic pain. Nature Reviews Neuroscience. 2017;18(1):20-30.
2. Bahm J, editor. Movement Disorders of the Upper Extremities in Children: Conservative and Operative Therapy. Springer Nature; 2021; 93-97.
3. Potharaju NR. Excessive crying in children with cerebral palsy with communication deficits-a fixed-sequence, crossover clinical trial. Glob J Res Anal. 2022; 11(07):25-44.
4. Eriksson E, Hägglund G, Alriksson-Schmidt AI. Pain in children and adolescents with cerebral palsy–a cross-sectional register study of 3545 individuals. BMC neurology. 2020; 20(1):1-9.
5. Ostojic K, Paget S, Kyriagis M, Morrow A. Acute and Chronic Pain in Children and Adolescents with Cerebral Palsy: Prevalence, Interference, and Management. Arch Phys Med Rehabil. 2020; 101(2):213-219.
6. Tedroff K, Gyllensvärd M, Löwing K. Prevalence, identification, and interference of pain in young children with cerebral palsy: a population-based study. Disability and rehabilitation. 2021; 43(9): 1292-1298.
7. Alriksson-Schmidt A, Hagglund G. Pain in children and adolescents with cerebral palsy: a population-based registry study. Acta Paediatr. 2016;105(6):665-670.
8. Novak I, Hines M, Goldsmith S, Barclay R. Clinical prognostic messages from a systematic review on cerebral palsy. Pediatrics. 2012;130(5):1285-1312.
9. Chanel Davidoff EL. Central Pain Syndromes. Pain Care Essentials and Innovations.2021.
10. UK NG. Cerebral palsy in under 25s: assessment and management.
11. Zochodne DW. The disrupted connectome and pain. Our Wired Nerves: The Human Nerve Connectome.155-171.
12. Blackman JA, Svensson CI, Marchand S. Pathophysiology of chronic pain in cerebral palsy: implications for pharmacological treatment and research. Dev Med Child Neurol. 2018;60(9): 861-865.
13. Hauer J, Houtrow AJ, Feudtner C, Klein S, Klick J, Linebarger J, et al. Pain assessment and treatment in children with significant impairment of the central nervous system. Pediatrics. 2017;139(6).
14. Fehlings D. Pain in cerebral palsy: a neglected comorbidity. Dev Med Child Neurol. 2017;59(8):782-783.
15. Tkacs N, Herrmann L, Johnson R, editors. Advanced Physiology and Pathophysiology: Essentials for Clinical Practice. Springer Publishing Company; 2020;1374-1569.
16. Westbom L, Rimstedt A, Nordmark E. Assessments of pain in children and adolescents with cerebral palsy: a retrospective population-based registry study. Dev Med Child Neurol. 2017;59(8): 858-863.

17. Jonas WB, Crawford C, Colloca L, Kriston L, Linde K, Moseley B, et al. Are Invasive Procedures Effective for Chronic Pain? A Systematic Review. Pain Med. 2019;20(7):1281-1293.
18. Fleischman AR. Children Are Special. Hard Questions, Hard Choices. Pediatric Ethics Protecting the Interests of Children.1:5-9.
19. Hagglund G, Burman-Rimstedt A, Czuba T, Alriksson-Schmidt AI. Self-versus Proxy-Reported Pain in Children with Cerebral Palsy: A Population-Based Registry Study of 3783 Children. J Prim Care Community Health. 2020;2150132720911523.
20. Speyer R, Cordier R, Kim JH, Cocks N, Michou E, Wilkes-Gillan S. Prevalence of drooling, swallowing, and feeding problems in cerebral palsy across the lifespan: a systematic review and meta-analyses. Dev Med Child Neurol. 2019;61(11):1249-1258.
21. Samal P, Goyal V, Makharia GK, Das CJ, Gorthi SP, Y VV, et al. Transfer Dysphagia Due to Focal Dystonia. J Mov Disord. 2018;11(3):129-132.
22. Tateishi Y, Ishikawa N, Tani H, Kobayashi Y, Kobayashi M. A Case in Which Oral Baclofen Was Effective for Dysphagia Associated With Acute Flaccid Myelitis by Enterovirus D68. Pediatr Infect Dis J. 2019;38(10):277.