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ORIGINAL RESEARCH

Pain reporting and analgesia management in 270 children with a progressive neurologic, metabolic or chromosomally based condition with impairment of the central nervous system: cross-sectional, baseline results from an observational, longitudinal study

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Abstract: Little is known about the prevalence, characterization and treatment of pain in children with progressive neurologic, metabolic or chromosomal conditions with impairment of the central nervous system. The primary aims of this study were to explore the differences between parental and clinical pain reporting in children with life-limiting conditions at the time of enrollment into an observational, longitudinal study and to determine if differences in pain experiences were associated with patient- or treatment-related factors. Pain was common, under-recognized and undertreated among the 270 children who enrolled into the "Charting the Territory" study. Children identified by their parents as experiencing pain (n=149, 55%) were older, had more comorbidities such as dyspnea/feeding difficulties, were less mobile with lower functional skills and used analgesic medications more often, compared to pain-free children. Forty-one percent of children with parent-reported pain (21.8% of all patients) experienced pain most of the time. The majority of clinicians (60%) did not document pain assessment or analgesic treatment in the medical records of patients who were experiencing pain. Documentation of pain in the medical record was positively correlated with children receiving palliative care services and being prescribed analgesics, such as acetaminophen, nonsteroidal anti-inflammatory drugs and opioids, as well as the adjuvant analgesics gabapentin and amitriptyline.

Keywords: pediatric palliative care, hospice, neuropathic pain, palliative, life-limiting

Plain language summary

To date, this prospective study is the largest study exploring pain in children with nonmalignant life-limiting diseases. Pain in children with progressive neurologic diseases was common, under-recognized and undertreated. Analgesia management in this vulnerable group currently lacks standard assessment tools, consensus treatment guidelines and prospective randomized controlled trials.

Introduction

Children living with serious illnesses commonly experience pain, which is among the most distressing and prevalent symptoms.[1–3] Nearly all studies of pain and other distressing symptoms in pediatric palliative care (PPC) were undertaken in children with

malignancies and show a significant symptom burden to this population.[4–7] However, the majority of children living with or dying from a serious illness do not have cancer.[8] In 2013, a total of 42,328 children aged 0–19 years died in the US, of whom >23,440 (55%) were infants <1 year of age. The most common life-limiting conditions for children living in the US include congenital malformations and chromosomal abnormalities (5,740) followed by malignancies (1,850).[9]

According to the Declaration of Montreal, access to pain management is a fundamental human right.[10] Yet, pain in hospitalized children in general, as well as in pediatric patients with advanced cancer, has been characterized as common, under-recognized and undertreated.[4–7,11–14] Existing data suggest that pain processing is altered in most individuals with cognitive impairment, compared with cognitively intact matched controls.[15] Nociception may be based on the underlying condition and/or treatment (including procedures/interventions) of that disease. Underlying pain pathologies in this group of nonverbal children with progressive neurologic, metabolic or chromosomal conditions, where the central nervous system (CNS) is impaired, often remain enigmatic. One might speculate that many of these children may have not one, but several underlying conditions simultaneously: acute somatic nociceptive pain (such as otitis media), visceral pain (such as bladder spasms, constipation), chronic postoperative pain,[16–19] autonomic disorders,[20] chronic pain beyond the expected time of healing or primary pain disorder (such as primary headaches, centrally mediated abdominal pain syndrome, chronic musculoskeletal pain),[21–25] medication overuse headaches,[26] visceral hyperalgesia,[27] psycho-social-spiritual pain and/or neuropathic pain.[20,28–30]

Little is known about pain prevalence, characterization and treatment in children with a progressive neurologic, metabolic or chromosomally based condition with impairment of the CNS. The primary aims of this study were to explore whether there were differences in pain experiences associated with patient- or treatment-related factors, and there were differences in parental and clinician pain reporting in children with life-limiting conditions at the time of enrollment into a prospective, observational, longitudinal study.

Methods

Data were obtained from a 3-year, multicenter, prospective cohort study of children living with progressive CNS conditions and their families (see Siden et al[31] for details regarding study design and methods). Subjects were recruited from clinics that followed patients with CNS conditions in nine child health centers (seven in Canada and two in the US). The conditions of interest were progressive, nontreatable and likely fatal; they affected the nervous system and potentially other organ systems. Children could be at any point in their disease trajectory. Extensive baseline information was obtained from a health records review by a trained research assistant and a baseline interview with a parent. Baseline data included a medication profile and list of interventions. From enrollment onward, monthly data on symptoms were obtained from parents. Follow-up information, including medications and interventions, was obtained either upon notification of the patient's death or at the time of the study's conclusion for those who were alive.

Additional information was acquired on an annual basis regarding the child's functional status and on a semi-annual basis for the psychosocial and health status of the parents and siblings. These data will contribute to other analyses and publications.

This study was approved by the University of British Columbia Clinical Research Ethics Board, whose approval jointly covered the BC Children's Hospital in Vancouver, BC. Further ethics approval was obtained at eight other clinical sites (six in Canada and two in the US) (see Supplementary Material section). In addition to obtaining ethical approval from each of the clinical study settings, ethical review and approval was also obtained from five universities at which the researchers were affiliated and/or their clinical hospices in which their primary clinical appointment resided. Confirmation of informed consent was provided by the parents or guardians of the children.

Analysis plan

In order to address the two aims of this paper, four separate analyses were undertaken. To explore whether there were differences in patient- or treatment-related factors associated with pain experiences of children with progressive neurologic, metabolic or chromosomal conditions, we used the following four frames: 1) exploring whether there were differences between children for whom parents reported pain during the baseline study interview versus those for whom pain was not reported; 2) for cases where parents reported their child was in pain, data were analyzed to determine if there were differences between children based on how often they were experiencing pain (most of the time vs. not most of the time); 3) for children whose parents reported pain, data were analyzed to determine if there were differences between children with pain documented in their medical record versus those without chart-documented pain and 4) differences between children by whether their pain was reported in the

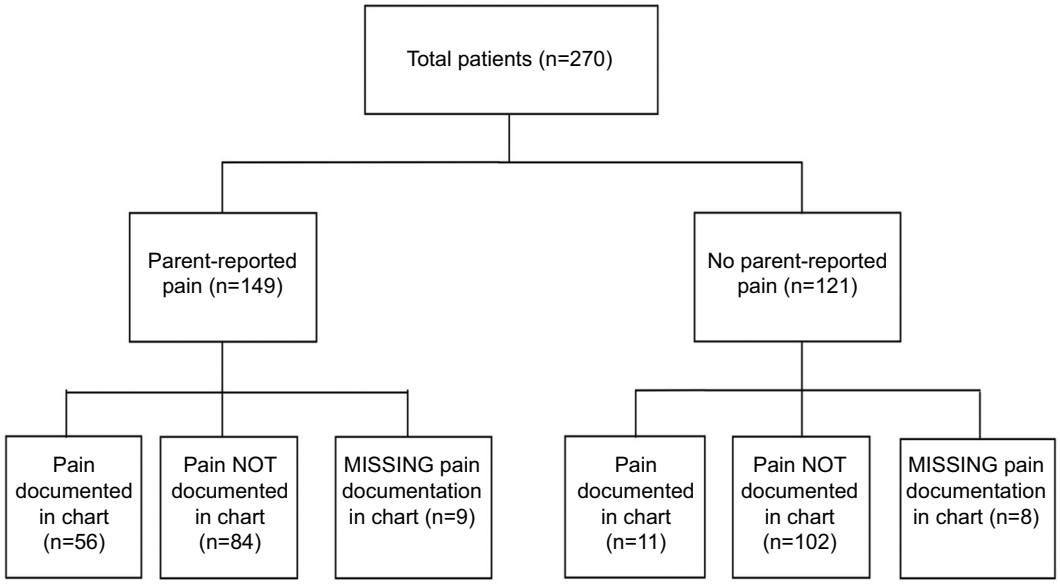

Figure 1 Study flow diagram organized by source of pain reporting.

medical record (yes/no) were explored, regardless of whether the parent reported pain. Figure 1 depicts pain reporting by the source of pain report (parent/medical record).

The following child characteristics (independent variables) were assessed: age, sex, ethnicity, PPC team involvement, income, parent education, pain percentage across lifetime, number of medication classes received, number of symptoms, number of disease groups, artificial feeding status (total parenteral nutrition [TPN], gastrostomy [G]-/jejunostomy [J]-tube or tube feeding), mobility/disability (Pediatric Evaluation of Disability Inventory [PEDI]),[32] do-not-attempt-to-resuscitate status, suctioning use and analgesia use (including opioids and adjuvant analgesia).

Statistical analysis

Medians and interquartile ranges were calculated for continuous variables because most were not normally distributed in this sample. Frequency distributions were calculated for categorical outcomes. Wilcoxon rank sum tests were used to determine whether statistically significant differences existed between the distribution of the comparison groups for continuous variables, and Pearson's chi-square tests or Fisher's exact tests, as appropriate, were used to evaluate the differences for all categorical outcomes.

Data from the multiple sites were entered into Daciforms, a web-based database (Dacima Software, Inc., Montreal, QC, Canada). From Daciforms, data were exported into SPSS v23 (IBM Corporation, Armonk, NY, USA). All analyses were performed using Stata SE version 14.[33]

Results

Differences between children with "no pain" versus "pain" as reported by parents at the time of study enrollment

At baseline (time of study enrollment), parents of 149/270 (55%) children reported their child was in pain. Children with parent-reported pain were significantly older (median=7.8 years [2.8, 12.0] vs. 5.3 years [2.8, 9.0], p=0.03), more likely to be from a lower-income household (p=0.04) and more likely to have dyspnea (30.7% vs. 19.5%, p=0.04) and feeding difficulties (48.9% vs. 31.0%, p=0.004) than the children whose parents did not report pain (Table 1).

Children with parent-reported pain were more likely than parents who indicated their child was not in pain to be receiving care from a PPC team (75.8% vs. 52.9%, p<0.001). They were also more likely to be prescribed the following classes of medications: antacids (54.1% vs. 36.4%, p=0.004), laxatives (41.2 vs. 28.1%, p=0.03), antispasticity medications (15.5% vs. 3.3%, p=0.001), acetaminophen/nonsteroidal anti-inflammatory drugs (NSAIDs; 25.0% vs. 10.7%, p=0.003), opioids (12.8% vs. 1.7%, p<0.001) and glucocorticosteroids (39.7% vs. 25.0%, p=0.03). When examined in more detail, children whose parents reported they were experiencing pain were more likely to be prescribed the World Health Organization (WHO)[34] step 1 basic analgesics (acetaminophen=20.9% vs. 7.4%, p=0.002; ibuprofen=11.5% vs. 4.1%, p=0.03), gabapentin as adjuvant analgesia (18.2% vs. 8.3%, p<0.02), and they were more

Table 1 Characteristics of children with progressive neurologic, metabolic or chromosomal conditions (PNC) at baseline by parent-reported pain status

Characteristics	PNC patients with baseline parent report			*p*-value[a]
	All patients, N=270	Pain, as per parent, n=149	No pain, as per parent, n=121	
Age (years) on entry to study, median (IQR: p25, p75)	5.9 (2.8, 11.2)	7.8 (2.8, 12.0)	5.3 (2.8, 9.0)	0.030
Age (months) at initiation of diagnostic evaluation, median (IQR: p25, p75)	2.7 (0, 11.8), n=256	2.4 (0, 12.7), n=140	3.5 (0, 9.2), n=116	0.994
Age (months) at diagnosis, median (IQR: p25, p75)	0.7 (0.1, 3.0), n=199	0.8 (0.1, 3.7), n=111	0.7 (0.1, 2.1), n=88	0.323
Sex, n (%)				
Female	137 (50.7)	75 (50.3)	62 (51.2)	0.883
Male	133 (49.3)	74 (49.7)	59 (48.8)	
Highest level of education reported by parent or guardian, n (%)				
High school or less	22 (8.2)	11 (7.4)	11 (9.1)	0.488[b]
High school diploma	27 (10.0)	14 (9.4)	13 (10.7)	
College or vocational school	103 (38.2)	63 (42.3)	40 (33.1)	
University or post graduate degree	118 (43.7)	61 (40.9)	57 (47.1)	
Household income (Canadian dollars), n (%)[c]	n=265	n=147	n=118	Overall 0.035
<$40,000	78 (29.4)	53 (36.1)	25 (21.2)	Reference
$40,000–<80,000	95 (35.8)	47 (32.0)	48 (40.7)	0.014
$80,000–<120,000	59 (22.3)	33 (22.4)	26 (22.0)	0.150
≥$120,000	33 (12.5)	14 (9.5)	19 (16.1)	0.012
PPC team involved (yes), n (%)	177 (65.6)	113 (75.8)	64 (52.9)	<0.001
Total number of symptoms other than pain present, median (IQR: p25, p75)	1 (0, 3)	2 (1, 3)	1 (0, 3)	0.006
Symptoms (yes), n (%)				
Dyspnea	65 (24.1)	43 (30.7), n=140	22 (19.5), n=113	0.042
Feeding difficulties	104 (38.5)	69 (48.9), n=141	35 (31.0), n=113	0.004
Alertness and interaction changes	38 (14.1)	22 (15.7), n=140	16 (14.2), n=113	0.731
Sleep problems	73 (27.0)	43 (30.9), n=139	30 (26.3), n=114	0.420
Seizures	108 (40.0)	66 (47.1), n=140	42 (36.8), n=114	0.099
Constipation	70 (25.9)	44 (31.4), n=140	26 (23.0), n=113	0.137
Artificial feeding in place (yes), n (%)				
TPN	4 (1.5)	4(2.7)	0	0.130[b]
G- or J- tube	145 (53.7)	91 (61.1)	54 (44.6)	0.007
N/G tube	16 (5.9)	11 (7.4)	5 (4.1)	0.261
Mobility, median (IQR: p25, p75)				
Functional skill, raw score	5 (2, 24), n=263	3 (1, 16), n=145	7.5 (2, 42), n=118	0.002
Mobility, count of extensive	0 (0, 2), n=262	0 (0, 3), n=145	0 (0, 2), n=117	0.021
DNAR or DNR order in place, n (%)				Overall 0.070
Yes	42 (15.6)	30 (20.1)	12 (9.9)	Reference
No	177 (65.6)	92 (61.7)	85 (70.2)	0.023
Unknown	51 (18.9)	27 (18.1)	24 (19.8)	0.069
Suctioning in place (yes), n (%)	49 (18.4), n=267	32 (21.8), n=147	17 (14.2), n=120	0.110
Basic analgesia used (yes), n (%)				
Acetaminophen	40 (14.9), n=269	31 (20.9), n=148	9 (7.4)	0.002
Ibuprofen	22 (8.2), n=269	17 (11.5), n=148	5 (4.1)	0.029
Adjuvant analgesia used (yes), n (%)				
Gabapentin	37 (13.8), n=269	27 (18.2), n=148	10 (8.3)	0.018
Amitriptyline	6 (2.2)	5 (3.4)	1 (0.8)	0.229[b]
Clonidine	4 (1.5)	3 (2.0)	1 (0.8)	0.630[b]
Opioids (opioids and simple analgesia) used (yes), n (%)	15 (5.6)	13 (8.7)	2 (1.7)	0.014[b]
Benzodiazepines used (yes), n (%)	109 (40.4)	66 (44.3)	43 (35.5)	0.145
Percent of pain during lifetime, median (IQR: p25, p75)	N/A	62.6 (10.9, 98.9), n=146	N/A	N/A

Notes: [a]Analyzed using Pearson's chi-square test for dichotomous variables or Wilcoxon rank sum tests for continuous variables, unless otherwise noted. [b]Analyzed using Fisher's exact test. [c]Currency conversion was not made for two US sites reporting income in US dollar categories, as the rates were near equivalent during the data collection period.

Abbreviations: DNAR, do not attempt resuscitation; DNR, do not resuscitate; IQR, interquartile range; N/A, not applicable; PNC, progressive noncurable conditions.

likely to be prescribed a combination of opioids and basic analgesics (8.7% vs. 1.7%, p=0.01).

When artificial feeding status and mobility were compared between groups, children with parent-reported pain were more likely to be receiving nutrition through a G- and/or J-tube (61.1% vs. 44.6%, p<0.01). When mobility status as measured by PEDI was examined, children with parent-reported pain were less mobile based upon how many modifications they required to be mobilized or transported (median [interquartile range {IQR}]: 0 [0, 3] vs. 0 [0, 2], p=0.02). Children with parent-reported pain also had lower functional skills compared to those whose parents did not report pain at baseline (PEDI raw functional skill score median [IQR]: 3[1, 16] vs. 7.5 [2, 42], p=0.002).

Finally, children whose parents reported pain were significantly more likely to have a do-not-attempt-to-resuscitate order in place (20.1% vs. 9.9%, p=0.02).

Differences between patients with "pain most of the time" versus "pain NOT most of the time" as reported by parents

Next, we examined data from the parents who reported their child was in pain at baseline (n=149) to determine if there were any differences between children who were in pain most of the time (n=60) versus not most of the time (n=88). One of the 149 parents did not report pain frequency, leaving 148 children included for this analysis. These groups did not differ sociodemographically. Less than half of parents (n=60, 41%) reported their child was in pain most of the time. However, children in pain most of the time were significantly more likely to be experiencing dyspnea (38.3% vs. 22.7%, p=0.04) and were less likely to be using "metabolic" medications such as carnitine, Coenzyme Q10, folic acid, omega-3 fish oil, cholecalciferol, and vitamins A, B6, C, E, K (28.3% vs. 47.1%, p=0.02). There were no other differences found between the groups for frequency of pain.

Children in pain at baseline according to their parents: comparison between those with and without clinician-entered pain documentation in chart

There were no sociodemographic differences between children whose pain was documented in their charts (n=56) compared to children whose pain was not documented in their charts (n=84) whose parents reported pain at baseline. Children with chart-documented pain were more likely to be receiving care from a PPC team than the children whose pain was only reported by their parents (i.e., not in the chart; 85.7% vs. 69.0%, p=0.02). In other words, children whose parents reported that they were experiencing pain were less likely to receive support from a PPC team if their pain was not also documented in their medical record (Table 2).

When symptom experience of children with parent-reported pain was compared between those with chart-documented pain and those without, the total number of symptoms present (other than pain) was significantly higher in the group of children with chart-documented pain (median [IQR]: 2[1, 4] vs. 1.5[1, 3], p=0.04). Children with chart-documented pain were significantly more likely to be experiencing dyspnea (41.1% vs. 23.8%, p=0.03) and changes in alertness/interaction (25.0% vs. 9.5%, p=0.01). Children with chart-documented pain were also more likely to be receiving TPN (7.1% vs. 0%, p=0.02), as shown in Table 2.

Children whose pain was reported by parents at baseline and whose pain was documented in their medical chart were more likely to be prescribed more classes of medications than those prescribed for children with parent-reported pain only (i.e., their pain was not captured in the medical chart; median [IQR]: 5 [3, 7] vs. 3 [2, 5], p<0.001). The following medication classes were prescribed significantly more often in these children with chart-documented pain: anxiolytics (57.1% vs. 37.3%, p=0.02), antacids (69.6% vs. 44.0%, p=0.003), laxatives (50.7% vs. 33.3%, p=0.02), WHO-step 1:[34] acetaminophen/NSAIDs (44.6% vs. 10.7%, p<0.001), WHO-step 2: opioids (25.0% vs. 3.6%, p<0.001) and other medications (53.6% vs. 35.7%, p=0.04), as shown in Figure 2. Finally, benzodiazepine use was higher in the children with chart-documented pain (57.1% vs. 36.9%, p=0.02).

Differences between children with or without pain as documented in their medical record

Regardless of whether parents reported pain for their child, of the 253 children with pain status data available in their medical record at baseline, pain was recorded for only 67 (26.5%) by a clinician (physician or nurse). The groups did not differ sociodemographically. Children with chart-documented pain were significantly more likely to be receiving care from a PPC team (83.6% vs. 59.7%, p<0.001) and to be experiencing more symptoms overall, not including pain (median [IQR]: 2 [1, 4] vs. 1 [0, 3], p=0.003). When we compared specific symptom experiences between groups, we found that children with pain documented in their charts were more likely to have dyspnea (40.3% vs. 20.4%, p<0.01) and feeding difficulties

Table 2 Characteristics of progressive neurologic, metabolic or chromosomal conditions (PNC) patients at baseline, comparison of chart documentation of pain for patients with parent-reported pain

Characteristics	PNC patients with parent-reported pain and available chart information, n=140		*p*-value[a]
	Chart-documented pain, n=56	No chart-documented pain, n=84	
Percent of pain during lifetime, median (IQR: p25, p75)	56.3 (15.0, 99.4), n=55	56.8 (4.7, 97.2), n=82	0.272
PPC team involved (yes), n (%)	48 (85.7)	58 (69.0)	0.024
Total number of symptoms other than pain present, median (IQR: p25, p75)	2 (1, 4)	1.5 (1, 3)	0.040
Symptoms (yes), n (%)			
Dyspnea	23 (41.1)	20 (23.8)	0.030
Feeding difficulties	32 (57.1)	37 (44.0)	0.129
Alertness and interaction changes	14 (25.0)	8(9.5)	0.014
Sleep problems	22 (39.3)	21 (25.0)	0.073
Seizures	25 (44.6)	41 (48.8)	0.629
Constipation	18 (32.1)	26 (31.0)	0.882
Total number of medication classes used,[b] median (IQR: p25, p75)	5 (3, 7)	3 (2, 5)	<0.001
Opioids used (yes), n (%)	14 (25.0)	3 (3.6)	<0.001[c]
Opioids plus basic analgesia used (yes), n (%)	8 (14.3)	3 (3.6)	0.027[c]
Basic analgesia used (yes), n (%)			
Acetaminophen	21 (37.5)	8 (9.6), n=83 6	<0.001
Ibuprofen	8 (14.3)	(7.2), n=83	0.175
Adjuvant analgesia used (yes), n (%)			
Gabapentin	17 (30.4)	8(9.5)	0.002
Amitriptyline	3 (5.4)	1 (1.2)	0.302[c]
Clonidine	2 (3.6)	1 (1.2)	0.564[c]
Artificial feeding in place (yes), n (%)			
Total parenteral nutrition	4 (7.1)	0	0.024[c]
G- or J- tube	38 (67.9)	46 (54.8)	0.121
N/G tube	4 (7.1)	7 (8.3)	1.000
Mobility, median (IQR: p25, p75)			
Functional skill, raw score	3 (1, 7), n=54	3 (1, 24), n=82	0.520
Mobility, count of extensive	0 (0, 3), n=54	0 (0, 2), n=82	0.778
DNAR or DNR order in place, n (%)			Overall 0.765
Yes	13 (23.2)	16 (19.0)	Reference
No	32 (57.1)	53 (63.1)	0.495
Unknown	11 (19.6)	15 (17.9)	0.851

Notes: [a]Analyzed using Pearson's chi-square test for dichotomous variables or Wilcoxon rank sum tests for continuous variables, unless otherwise noted. [b]Does not include "Other" medications as a class. [c]Analyzed using Fisher's exact test.

Abbreviations: DNAR, do not attempt resuscitation; DNR, do not resuscitate; G, gastrostomy; IQR, interquartile range; J, jejunostomy; N/G, nasogastric; PNC, progressive noncurable conditions.

(55.2% vs. 37.2%, p=0.01) documented, as compared to children without chart-documented pain.

Children with chart-documented pain were more likely to be prescribed medications representing a wider range of medication classes (median [IQR]: 5 classes [3, 7] vs. 3 classes [1, 4], p<0.001). Specifically, children assessed by a clinician as experiencing pain were more likely to be prescribed anxiolytics (55.2% vs. 34.2%, p=0.003), antacids (65.7% vs. 38.7%, p<0.001), laxatives (50.7% vs. 29.8%, p=0.002), antispasticity medications (17.9% vs. 6.8%, p=0.008), acetaminophen/NSAIDs (43.3% vs. 9.4%, p<0.001), opioids (22.4% vs. 2.1%, p<0.001), glucocorticosteroids (47.5% vs. 28.4%, p=0.01) and other medication classes (55.2% vs. 33.5%, p=0.002). Basic WHO-step 1 analgesia (ibuprofen and acetaminophen) was significantly more likely to be prescribed for children with chart-documented pain (acetaminophen=35.8% vs. 7.4%, p<0.001; ibuprofen=14.9% vs. 4.7%, p=0.006). Adjuvant analgesia was more highly prescribed for children who had clinician-documented pain, with both gabapentin (28.4% vs.

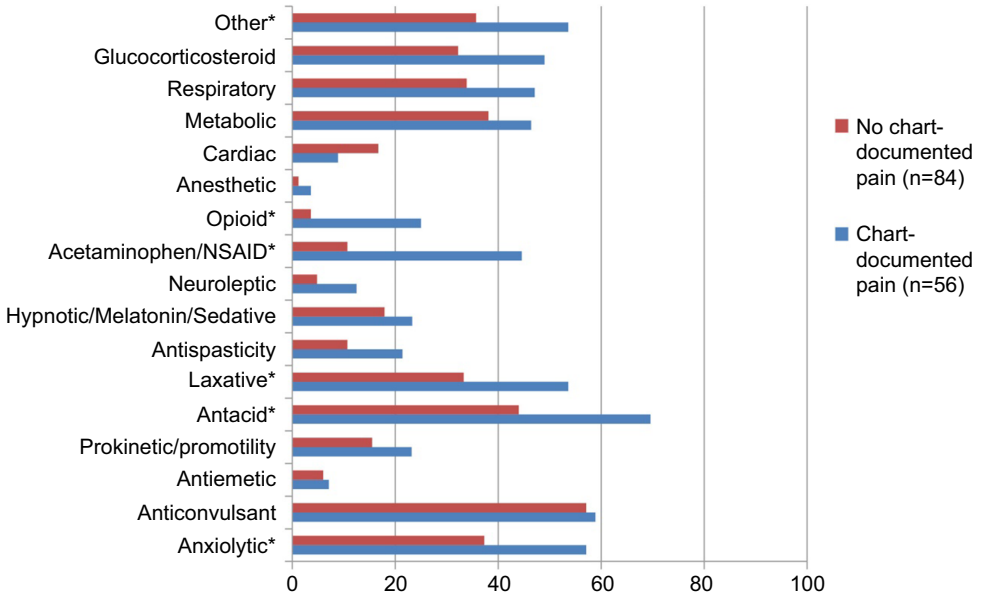

Figure 2 Percentage of pain and symptom medications prescribed for children whose parents reported pain, by whether or not pain was reported in their medical chart (n=140).
Notes: *p value <0.05. For the anxiolytic medication comparison, n=83 for the group with no chart-documented pain due to one missing value. For respiratory medications and corticosteroids comparisons, n=51 for the group with chart-documented pain due to missing values.
Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

17.9%, p<0.001) and amitriptyline (6.0% vs. 0.5%, p=0.017) being prescribed significantly more often. A combination of WHO-step 2 opioids and WHO-step 1 basic analgesia (i.e., acetaminophen or ibuprofen) was prescribed more often for children with chart-documented pain, compared to those without chart-documented pain (13.4% vs. 2.1%, p=0.001).

Artificial feeding devices were significantly more likely to be in place for children with chart-documented pain. Specifically, children with clinician-documented pain were more likely to be receiving TPN (6.0% vs. 0%, p=0.004) and were more likely to be dependent upon a G- and/or J-tube for nutrition (64.2% vs. 49.7%, p=0.04) than those without chart-documented pain. In terms of advanced planning, do-not-resuscitate orders were significantly more likely to be in place for children whose pain was documented in the chart (23.9% vs. 13.6%, p<0.05).

Discussion

To date, this prospective cohort study is the largest to explore prevalence, assessment and treatment of pain in children with life-limiting nonmalignant diseases. Pain was common, under-recognized and undertreated among the 270 children from Canada and the USA who were suffering from neurologic, genetic or metabolic conditions with impairment of the CNS.

Overwhelmingly, published evidence of pain prevalence, assessment and treatment in PPC focuses on children with a malignancy and there is a dearth of research on pain in children with life-limiting, nonmalignant diseases. A prospective study describing patient-reported outcomes in pediatric patients with advanced cancer showed that 39% of all children were self-reporting high distress from pain, which increased to 58% at the end of life.[7] However, the majority of children living with, and dying of, life-limiting diseases do not have cancer.[8] Higher pain prevalence rates than in the normal pediatric population have been reported in children with developmental disabilities,[35,36] cerebral palsy,[37,38] Noonan syndrome,[39,40] progressive neurodegenerative and metabolic conditions,[41–43] as well as in children dying of nonmalignant diseases.[44,45] In 2011, data from an observational cohort study of 515 patients served by six PPC teams in North America showed that 31% of the children experienced pain at the time of consultation.[3] The predominant primary clinical conditions of these children were genetic/congenital (41%), neuromuscular (39%), followed by cancer (20%).

The majority of the 270 children with progressive neurologic, metabolic or chromosomal conditions in our study experienced pain (n=149, 55%) at the time of study enrollment according to their parents. The analysis of all 149 children experiencing parent-reported pain revealed that they were significantly more likely to have received PPC services, to have been more symptomatic (increased dyspnea and changes in alertness/interaction), to have received TPN and to have received basic analgesics, opioids and benzodiazepines.

In our study, children experiencing parent-reported pain were more likely than those without pain to receive artificial nutrition and hydration through a G- or J-tube. Children receiving enteral tube feeding usually have a higher morbidity and appear more prone to developing feeding intolerance and/or visceral hyperalgesia.[46,47] Pain caused by artificial feeding, unresponsive to conservative intervention, appears to be a leading symptom, suggesting that a child with advanced serious illness may have entered the end-of-life period.[48] Compared to children without pain, children with parent-reported pain were more likely to use the WHO pain ladder[34] of basic (acetaminophen, NSAIDs) and opioid analgesics in our study. Also, adjuvant analgesia, especially gabapentin,[49] was used significantly more often. However, other adjuvants, which might play a role especially in the pharmacologic treatment of neuropathic and/or visceral pain[50–53] (such as the alpha-agonists[54–56] clonidine or dexmedetomidine, tricyclic antidepressants[57,58] such as amitriptyline or nortriptyline, *N*-methyl-D-aspartic acid-channel blockers[59,60] such as ketamine or methadone and sodium channel blockers such as lidocaine[60–63]) were rarely administered to the children in pain in this study. This finding points to a paucity of evidence and established treatment guidelines in the management of these challenging patients.

Our study also showed that children with parent-reported pain were sicker and of lower socioeconomic status than the children who were pain free. They were more likely to be from low-income households and to have associated comorbidities such as dyspnea, impaired mobility, lower functional skills and feeding difficulties. Health disparities are well described in the literature, and income differences correlate strongly with health outcomes among children. For instance, families with low incomes have a higher prevalence of abdominal pain among their children with increased pain intensity.[64,65] Our results support existing literature on differences in health outcomes due to socioeconomic status.[48,53,66–70]

Due to their CNS impairment, self-report was not feasible, but more than one out of five parents reported pain as occurring most of the time. Stallard et al reported a similar number in a small study, with 8 (23.5%) out of 34 cognitively impaired, noncommunicating children experiencing daily pain according to their parents.[36] The children in our study who experienced pain most of the time were more likely to experience dyspnea, suggesting a higher morbidity.

The 67 children with pain documentation in their charts compared to patients who did not have any pain documented by clinicians were more likely to experience more distressing nonpain symptoms, including dyspnea and feeding difficulties, in our study, and they were more likely to have a G- or J-tube. They were more likely to receive basic analgesics (acetaminophen, NSAIDs), opioids and adjuvant analgesia (gabapentin and amitriptyline), as well as benzodiazepines, glucocorticosteroids and muscle relaxants. In addition, among the study patients, documentation of pain was correlated with a higher likelihood of children receiving care from a PPC team and to have a do-not-resuscitate order. It would be difficult to extrapolate causality: one might speculate that the inclusion of a PPC team might result in increased pain assessment and analgesic prescription, and/or that the realization of increased pain and symptom burden result in children with serious illness increases the chance of referral to a PPC team.

One surprising finding was that for over half (56%) of cases in which parents reported their child was experiencing pain at baseline, no associated pain documentation was found in the child's medical chart. Data suggest that pain assessment is critical to optimal pain treatment interventions and that the assessment and documentation of pain results in increased prescription of analgesics.[34,71–74]

Unlike in adult patients with neuropathic, visceral and/or chronic pain, there are no guidelines, randomized controlled trials or systematic reviews guiding the assessment and treatment of this challenging pediatric population.[50,75,76] One may speculate whether lack of pain documentation might be due to missing pain assessment standards, guidelines and/or lack of knowledge about how to differentiate and treat acute nociceptive, visceral, neuropathic, psycho-social-spiritual or chronic pain in seriously ill children suffering from pain. Abdominal discomfort appears to be a common complaint in these children as reported by parents, and feeding intolerance and visceral hyperalgesia[27] may not be uncommon. In nonverbal, cognitively impaired children, pain assessment and the ability to differentiate between "episodes of inconsolability", "neuroirritability" and "pain" remain difficult. Autonomic stress response (i.e., change of heart rate, heart rate variability, mean arterial blood pressure, respiratory rate, plasma levels of norepinephrine and epinephrine) is not significantly correlated with pain severity.[77] The absence of signs of sympathetic stimulation cannot be accepted as a guarantee for the absence of significant pain, and traditional pain assessment cannot be replaced with more objective measures of physiologic changes of autonomic and respiratory parameters.[78] Validated pain assessment tools for children with impaired communication are available, but are not commonly used in daily practice.[79–84] The findings of this study suggest that the lack of appropriate measurement tools is not a barrier to pain

assessment by clinicians. Further studies need to determine what system issues limit their use.

Supported by adult and pediatric evidence,[85,86] advanced pain treatment postoperatively and also for complex children with advanced serious illnesses is increasingly based on the opioid-sparing concept of "multimodal analgesia":[53] Multiple pharmacologic agents (such as basic analgesics, opioids and adjuvant analgesia), regional anesthesia (such as central neuraxial infusions, peripheral nerve and plexus blocks or infusions, neurolytic blocks and implanted intrathecal ports and pumps for baclofen, opioids, local anesthetics and other adjuvants),[87] rehabilitation (such as physical, occupational, speech and music therapy),[88,89] psychologic family therapy[90–92] and integrative therapies[93–95] (such as massage, deep breathing, aromatherapy, yoga), act synergistically for more effective pediatric pain control with fewer side effects than a single analgesic or modality. Although we could describe a higher use of analgesia and adjuvant pain medication in children referred to PPC in our study population, future research is required to evaluate the efficacy and safety of multimodal analgesia in children with progressive, neurodegenerative and chromosomal conditions with impairment of the CNS.

Study limitations

Our study population is heterogeneous in terms of age, underlying condition and disease progression. This heterogeneity complicates intergroup comparisons and interpretation of results. However, many of the conditions in our study population are so rare that it would not be feasible to enroll a sufficient number of children with the same condition and similar disease progression. Also, the timing of a child's medical visit with respect to the baseline study interview with the child's parent varied, although the timing of the clinical assessment was as close as possible to the parent pain assessment. Finally, parent proxy ratings of pain were used instead of child self-report, as the cognitive impairment of the mostly nonverbal children excluded self-reporting.

Conclusion and implications

Pain in children with progressive neurodegenerative/chromosomal conditions with CNS impairment is common, under-recognized and undertreated. In our cohort, children who experienced parent-reported pain were prescribed more comprehensive health services, including analgesia and PPC services, when their pain was documented in their medical record by a clinician. Further research should address the gap in pain recognition and reporting in this population of children, in order to ensure optimal pain management throughout their disease trajectory. Clinicians treating this challenging population lack standard assessment tools for pain, consensus treatment guidelines and evidence from prospective randomized controlled trials. Future research should evaluate whether effective prevention and treatment of pain in this large group of children might be more effective if it employs multimodal analgesia strategies.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

List of IRBs and Ethics Committees

Study sponsor: Canadian Institutes of Health Research (CIHR MOP-89984)

Participating sites

1. Calgary (Alberta Children's Hospital – Dr Sharron Spicer) – The Conjoint Health Research Ethics Board (CHREB) (University of Calgary)
2. Edmonton (Stollery Children's Hospital – Dr Dawn Davies) – Health Research Ethics Board (University of Alberta)
3. Toronto (The Hospital for Sick Children – Dr Adam Rapoport) – Research Ethics Board (SickKids)
4. Ottawa (Children's Hospital of Eastern Ontario – Dr Christina Vadeboncoeur) – Research Ethics Board (CHEO Research Institute)
5. Montreal (Montreal Children's Hospital – Dr Stephen Liben – Research Ethics Board (McGill University Health Center)
6. Vancouver – The University of British Columbia/Children's and Women's Health Centre of British Columbia Research Ethics Board (UBC C&W REB)
7. Halifax – Research Ethics Office (IWK Health Centre Research)
8. Gillette Children's in St Paul – Institutional Review Board (IRB) (University of Minnesota)
9. Children's Hospitals and Clinics of Minnesota – Institutional Review Board (IRB) (Children's Hospitals and Clinics of Minnesota)

Institutions

1. York University ON – Office of Research Ethics (ORE), Human Participants Review Sub-Committee
2. UCSF – Committee on Human Research (CHR)
3. UVIC – Human Research Ethics Board (HREB)
4. U Waterloo – Office of Research Ethics
5. Laurier – Research Ethics Board (Wilfrid Laurier University)

Hospices

Canuck Place Children's Hospice Ethics Committee