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Neuropathic Pain Referrals to a Multidisciplinary Pediatric Cancer Pain Service

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Abstract

Objectives—Neuropathic pain (NP) in children with cancer is not well characterized. We describe the prevalence of NP and the characteristics, duration of follow-up, and interventions provided for NP among patients referred to a pediatric oncology center's pain management service.

Methods—Retrospective review of patient data from a 3.5-year period.

Results—Fifteen percent (66/439) of all referrals to our pain service were for NP (56/323 patients, 17%; 34 male, 22 female). The NP patient group had 1401 clinical visits (778 inpatient visits [55.5%] and 623 outpatient visits [44.5%]). Patients with NP had a significantly greater mean number of pain visits per consult ($p=0.008$) and significantly more days (median) of pain service follow-up ($p<0.001$) than did other patients. The most common cause of NP was cancer treatment rather than the underlying malignancy. Pharmacological management of NP was complex, often comprising 3 medications. Nonpharmacological approaches were used for 57.6% of NP referrals.

Discussion—NP is less frequently encountered than non-NP in children with cancer; nevertheless, it is more difficult to treat, requiring longer follow up, more clinical visits, complex pharmacological management, and the frequent addition of non-pharmacological interventions.

Keywords

neuropathic pain; pediatric oncology

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Introduction

Neuropathic pain (NP) is pain directly caused by a lesion or disease affecting the somatosensory system (Treede, et al., 2008). NP is encountered less often than nociceptive pain and is more difficult to treat (Berger, et al., 2004; Grond, et al., 1996; Walco, et al., 2010). NP can impair quality of life by causing suffering and by reducing the patient's ability to function and perform normal activities of daily living (Hudson, et al., 1998; Jensen, Finnerup, 2007; O'Connor, 2009).

Experience of pain early in life may permanently alter pain-related behavior and perception (Howard, 2003). Pediatric oncology patients can experience NP through tumor invasion of the spinal cord or nerve roots (Collins, et al., 1996), amputation (Krane, Heller, 1995; Melzack, et al., 1997), limb-sparing surgery (Swarm, et al., 2010), chemotherapy (Anghelescu, et al., 2011), radiation therapy (Bleyer, et al., 2009), or hematopoietic stem cell transplantation (HSCT) (Grond, et al., 1996). Although children are known to experience NP, most of the available literature describes adults. Few systematic studies have been reported in pediatric patients. Attempts to compare pediatric and adult NP have suggested that substantial differences are to be expected in prevalence, symptoms, duration, recurrences, and response to different treatments; therefore, further research is necessary (Walco, et al., 2010).

Here the characteristics of oncology patients referred to a pediatric cancer center pain management service and diagnosed with NP are described, along with the prevalence of NP among pain service referrals, the duration of follow-up and the pharmacological and non-pharmacological interventions provided for NP management. This study tests the hypothesis that NP is less common than non-NP in pediatric cancer patients, requires longer follow-up, is more difficult to treat, and requires multimodal therapy that often comprises both multiple drugs and non-pharmacological approaches.

Methods

This retrospective review was approved by the St. Jude Children's Research Hospital Institutional Review Board. A prospectively maintained Pain Service database captures all referred patients, each encounter with the Pain Service, patient characteristics (age, sex, oncological diagnosis, and cause of pain), the specific pain diagnosis for each pain service visit (NP, nociceptive pain, mixed nociceptive and neuropathic pain) and pharmacological and non-pharmacological therapies.

The database was retrospectively analyzed to determine the total number of patient referrals to the Pain Service between January 2001 and June 2004, the number of Pain Service visits per patient and per referral, the treatment prescribed, and the duration of follow-up (inpatient and outpatient). The number of patient referrals was used to generate the incidence of NP vs. non-NP in the patient population followed by the Pain Service; the number of Pain Service visits was used to calculate the number of visits per patient and per referral. A clinical visit was defined as any inpatient or outpatient encounter with the Pain Service physician and/or clinical nurse specialist. Some patients were treated for a pain event during the study period and then discharged. If these patients were subsequently referred to the Pain Service during the study period, they were counted as new referrals. The duration of pain service follow-up was defined as number of days between the initial consultation provided by the pain service and the last visit, when the patient was discharged from the pain service.

Patient referrals were categorized by type of pain (NP and non-NP). Any patient with a NP component, including those with mixed NP and nociceptive pain, was included in the NP category. The diagnosis of NP was established based on at least one of the following criteria: 1) presence of pain descriptors suggestive of NP, such as burning, tingling, shooting, “needles and pins”; 2) distribution of pain suggestive of irradiation along the anatomic distribution on a nerve; 3) association with a clinical circumstance which is known to be a generator of neuropathic pain, such as: administration of chemotherapy (vincristine), postoperative pain following surgery associated with mechanical nerve trauma (limb sparing surgery) or with severing of nerves (amputation). Any one or more of these diagnostic criteria are taken into consideration when establishing the diagnosis of NP in children in our practice. In preverbal children, we had to rely mostly on the third criterion to diagnose NP. Additional diagnostic imaging data (i.e. mass compressing the spinal cord or nerve roots) is considered in support of establishing the diagnosis of NP in children who present with pain but cannot report the characteristics or distribution of pain. The diagnosis of NP was reevaluated at each pain service visit and included in the documentation reflecting pain assessment for each visit.

Patient characteristics and pharmacological and non-pharmacological therapies were collected from the pain service database and the medical records. Data were collected by using a standardized case report form developed by the investigators and were analyzed by using descriptive statistics. We used the one-sample t test and the Wilcoxon signed rank test to compare the number of encounters per referral and the duration of follow-up for NP vs. non-NP patients on the Pain Service, respectively.

Results

Between January 2001 and June 2004, the Pain Service accepted 439 referrals of 323 patients. Fifty six (17%) of these patients had NP (34 male and 22 female), and 66 referrals (15%) were for NP. The median age of patients with NP was 16 years (range, 2.2 – 28.2 years), and the median age of non-NP patients was 13.9 years (range, 0.3-37.5 years). The patients over 20 years of age in the NP and non-NP groups represented 16% (9 of 56) and 13.2% (37 of 281), respectively. The majority of NP patients had a solid tumor diagnosis (37 of 56, 66.1%); most of the solid tumors (24/37) were osteosarcoma (Table 1). The most common cause of NP was limb-sparing surgery, followed by chemotherapy (Table 2). In all but one case, patients referred more than once had the same causative condition for all referrals; one patient who had NP after limb-sparing surgery also experienced NP 6 months later after undergoing thoracotomy.

The total number of referrals, mean number of visits per referral, and median duration of follow-up on the Pain Service comparing the frequency of visits for patients with NP to those with nociceptive pain are shown in Table 3. The NP patient referrals generated 1401 clinical visits, 778 (55.5%) of which were inpatient and 623 (44.5%), outpatient. The mean number of visits per referral was 21.2 for NP and 14.1 for non-NP ($p=0.008$ one-sample t test).

The median (range) duration of follow-up on the Pain Service was 10 (1-553) days; median (range) of follow-up was 36 (1-537) days for NP referrals and 7 (1-553) days for non NP referrals ($p<0.001$, Wilcoxon signed rank test).

All patients referred for NP received at least one pharmacologic intervention, most commonly opioids (97% of NP referrals), followed by anticonvulsants (usually gabapentin) (90.9% of NP referrals). Almost all patients (58 of 66 referrals, 87.9%) received a regimen based on both opioids and an anticonvulsant (most often gabapentin), and 24 of 66 referrals

were also treated with a tricyclic antidepressant (amitriptyline). Data demonstrating single-agent versus multiple-agent therapies are presented in Table 4. Non-pharmacological pain management (frequently a combination of psychological interventions and physical therapy) was used in addition to medication in 38 of 66 NP referrals (57.6%).

Discussion

In this study, 17% of the patients referred to our pediatric oncology pain service had NP or a mixture of NP and nociceptive pain. These patients required longer follow-up and more numerous follow-up visits than did patients with nociceptive pain. Neuropathic pain was most commonly caused by treatment rather than by the underlying disease. Almost all referrals received a regimen based on both opioids and an anticonvulsant (most often gabapentin), and one third of referrals were also treated with a tricyclic antidepressant (amitriptyline).

The clinical diagnosis of NP in children is difficult to establish and there are no standardized tools to diagnose NP in children. In our study, we applied three clinical diagnostic criteria for NP, as presented in the methods section. In the subset of pediatric patients who cannot self-report, we encourage the use of the criterion of association with a clinical circumstance which is known to be a generator of neuropathic pain, such as: administration of chemotherapy (vincristine), postoperative pain following surgery associated with mechanical nerve trauma (limb sparing surgery) or with severing of nerves (amputation). In a study of NP in children with acute lymphoblastic leukemia, vincristine-related NP was defined by both a time relationship with the administration of vincristine within the previous 7 days of the onset of pain, and descriptors of quality of pain suggestive of NP (burning, shooting, tingling, “needles and pins”) (Anghelescu, et al., 2011). Furthermore, one could support the rationale of using diagnostic imaging data to support the diagnosis of NP, such as scans suggestive of tumor impinging on the spinal cord or nerve roots. In a preverbal child who cannot provide descriptors of pain quality indicative of NP, in the presence of suggestive diagnostic imaging, clinicians can establish a presumptive diagnosis of NP and treat as such.

Although several studies of pediatric cancer pain have been reported, many did not separate NP and non-NP (Elliott, et al., 1991; Ljungman, et al., 2000). In one comparable study of 84 pediatric outpatients with cancer pain, 14% had NP (Mishra, et al., 2009) a proportion very similar to our findings (17%). In one study of children with leukemia, only 5% of patients had neuropathic pain (Geeta, et al., 2010); however, in another study, 34.9% of children with leukemia had chemotherapy-related NP (Anghelescu, et al., 2011). Larger studies have been performed in adults. In one prospective study of 2266 adult cancer patients referred to a pain service, 34% had NP (Grond, et al., 1996).

In this study, the disease process was the cause of NP in only approximately 10% of patients; the vast majority experienced treatment-related NP. Other investigators who grouped all types of pain together have reported similar results in pediatric oncology patients (Elliott, et al., 1991; Ljungman, et al., 2000; Miser, et al., 1987). Conversely, adult oncology studies that specifically examined the causes of NP found the majority of NP to be caused by the disease rather than by treatment (Grond, et al., 1996; Grond, et al., 1999; Stute, et al., 2003). This is the first study that has found that neuropathic pain in pediatric cancer is predominantly treatment-related.

Patients with NP required longer follow-up and more numerous visits before discharge from the pain service than did patients with non-NP. This finding is consistent with our clinical impression that NP is more difficult to treat and consumes more resources than non-NP. One

adult study reported substantially higher health costs for patients with painful neuropathic disorders as compared to matched controls (Berger, et al., 2004).

Multimodal therapy was standard in this cohort of patients with NP; almost all patients received opioids and gabapentin, and approximately one third were also treated with amitriptyline. Our routine practice is to provide opioids for the treatment of NP, in addition to anticonvulsant therapy (gabapentin) and/or tricyclic antidepressant (amitriptyline). This practice is supported by the literature. In a Cochrane database systematic review of opioids for NP, intermediate-term trials (median 28 days, range 8 to 70 days) have demonstrated consistent opioid analgesic efficacy in reducing spontaneous NP; when results were pooled, this reduction was statistically significant (Eisenberg, et al., 2006).

Furthermore, opioids have a unique place among NP medications. Opioids are considered second line therapy for NP, except for selected clinical situations, when they are indicated as first line therapy: 1) acute NP, 2) episodic exacerbations of NP, 3) cancer-related NP, 4) during titration of a first line medication (O'Connor, Dworkin, 2009). Only one other pediatric oncology study has examined treatment strategies for NP; although the study design did not allow direct comparison, adjuvant drug usage was minimal (Zernikow, et al., 2006). In a study of NP in adults with cancer, only about half of patients received adjuvant drugs (Grond, et al., 1999). Another adult study showed that adjuvant drugs were used in approximately 70% of patients (Mishra, et al., 2008).

Psychological evaluation and treatment was provided for 38 referrals (57.6%). Reasons for not receiving this service included patient or family refusal, or non-English speaking background. Neuropathic pain can have a severe negative impact on a patient's ability to function independently, succeed in school, and participate in activities with family and peers. A variety of psychological treatments are typically used; cognitive-behavioral techniques have been found to be most effective (Haythornthwaite, Benrud-Larson, 2001; Molton, et al., 2007; Turk, et al., 2010). While few reports specifically address the use of psychological treatments in children with cancer suffering from NP, psychological techniques are commonly used for other types of acute and chronic pain in the pediatric population (Eccleston, et al., 2002; Palermo, et al., 2010; Walco, et al., 1999) and have been used successfully in adults to reduce NP (Daniel, et al., 2008; Haythornthwaite, Benrud-Larson, 2001; Oneal, et al., 2008; Turk, et al., 2008).

The key limitation of our study is the retrospective design. Ideally, the investigators would determine the length of time patients were on each medication, the dosage, the analgesic effectiveness of the treatment, and the timing of the resolution of pain and the weaning of medication. A record of pain scores and concomitant medication dosage would have provided information about how well pain was treated. We were also unable to separate inpatient from outpatient treatment with the available data, and this information might have been useful. The number of visits per patient and per referral may be artificially increased by the system of daily evaluations for inpatients; nevertheless, this method did not affect the comparison between groups, since it was applied to all patients. Due to the nature of our population, we provide long term care to cancer survivors; this explains the range of ages in our patient population and the inclusion of young adults in addition to children and adolescents. The age of our data is a potential limitation; nonetheless, the findings are informative in view of the paucity of data in pediatric neuropathic pain.

This investigation can serve as a starting point for future studies on NP in children and for utilization review and budget and billing purposes. Pediatric NP is a heterogeneous group of pain entities; specific research questions may address underlying conditions, genetic factors,

and the value of preventive interventions and treatment strategies so that clinical practice can evolve from “one size fits all” to more effective, individualized treatments.

In conclusion, at our children’s cancer hospital, children and young adults with neuropathic pain represent only 15% of referrals to the pain service. This pain diagnosis requires significantly longer follow-up, more visits per referral, and treatment with an average of 3 medications; nonpharmacological interventions are used in more than half of the referrals. A validated tool for diagnosing and measuring NP in young patients is needed to better understand this pain entity. Prospective multi-institutional studies in children with neuropathic pain are necessary to identify the therapeutic regimens with best analgesic efficacy.

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Table 1

Primary Oncology Diagnosis of 56 Pediatric Patients Referred to the Pain Service for Neuropathic Pain

Diagnosis	N (%)
Osteosarcoma	24 (42.9)
Ewing sarcoma	8 (14.3)
Acute lymphoblastic leukemia	6 (10.7)
Acute myeloblastic leukemia	4 (7.1)
Non-Hodgkin lymphoma	4 (7.1)
Brain tumor	4 (7.1)
Sarcoma	2 (3.6)
Synovial sarcoma	1 (1.8)
Osteochondroma	1 (1.8)
Rhabdomyosarcoma	1 (1.8)
Hodgkin lymphoma	1 (1.8)

Table 2

Source of Neuropathic Pain in 56 Patients

Source of pain	Patients (n=56) ^a	Consults (n=66)
Limb-sparing surgery	26	27
Chemotherapy	15	20
Amputation	8	9
Tumor	5	7
Other postoperative pain	2	2
Radiation	1	1

^a All recurring consults resulted from the same source of pain as the original consult, except one patient referred twice for two distinct sources of pain, 6 months apart.

Table 3

Number of Pain Service Referrals, Number of Visits, and Duration of Follow-Up

	Number of referrals (%)	Number of patients (%)	Duration of follow up: median (range) days	Number of visits: mean
All referrals	439	323	10 (1-553)	13.9
NP referrals	66 (15.0)	56 ^a (17.3)	36 (1-537)	21.2
Non-NP referrals	373 (85.0)	281 ^a (87.0)	7 (1-553)	14.1

^a Some patients had separate consult(s) for NP and non-NP indications during the study period.

Table 4

Pharmacologic Therapies Prescribed in 66 Referrals for Neuropathic Pain

Single Agent, n (%)	5 (7.6%)
Opioid only	4
Gabapentin only	1
Two Agents, n (%)	36 (54.5%)
Opioid + anticonvulsant	33
Opioid + TCA	1
Opioid + lidocaine patch	1
Gabapentin + methadone	1
Three Agents, n (%)	23 (34.9%)
Opioid + anticonvulsant + TCA	22
Opioid + anticonvulsant + lidocaine patch	1
Four Agents, n (%)	2 (3.0%)
Opioid + gabapentin + TCA + mexilitine	1
Opioid + gabapentin + TCA + methadone	1

TCA= tricyclic antidepressants