University of Cincinnati

Date: 3/26/2014

I, Sarah E Stueber, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Impact of Plexiform Neurofibromas in Adult Patients with Neurofibromatosis Type 1

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This work and its defense approved by:

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Committee member: Elizabeth Schorry, M.D.
Impact of Plexiform Neurofibromas in Adult Patients with Neurofibromatosis type 1

A thesis submitted to the
Graduate School
of the University of Cincinnati
in partial fulfillment of the
requirements for the degree

Master of Science

in the department of Pediatrics
of the College of Medicine
April 3, 2014
by
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BS, Wittenberg University, 2012

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Lisa Martin, PhD
Katie Wusik, MS
Abstract

Neurofibromatosis type 1 (NF1) is one of the most common autosomal dominant genetic conditions diagnosed today. Up to 50% percent of patients with NF1 will develop a specific type of neurofibroma tumor called plexiform neurofibromas (PNFs). PNFs develop along the nerve endings in individuals with NF1 and may develop along multiple nerve systems. Though typically benign, these tumors can cause significant complications. However, little is understood about the natural history of NF1 with PNF. This study was a retrospective chart review of adult patients that investigated rates of surgery and development of malignancy in patients with NF1 and PNF. Results demonstrated that patients with greater numbers of PNFs were more likely to have surgery (p = 0.02). PNFs located in the head and neck and paraspinal region had higher frequency of surgeries compared to those located in the pelvis or extremities (p = 0.026). In our patient population malignancies arising from PNFs were significantly more likely to occur in a core location as opposed to in the extremities or head/neck (P<0.05). Taken together these results suggest that the adult population has significant tumor morbidity associated with PNFs in relation to surgery rates and malignancies. Thus, this study highlights the need of adult NF patients with PNF to have ongoing monitoring of their tumors. Future studies will be needed to determine modality and intervals of screening for best outcomes.
Acknowledgements

I would like to acknowledge my Research Advisor and Research Committee for all of their assistance and hard work through this process. I would also like to thank Anne Lovell for her help during this research.
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Background

Neurofibromatosis is one of the most commonly diagnosed genetic conditions by clinicians worldwide (Sideras et. al, 2013). The prevalence of NF1 is currently estimated at one in every 2,500, people (Evans et. al, 2010). This disease affects many people and has extremely variable expressivity. Some patients have minimal or cosmetic-only complications, whereas others experience many debilitating complications including, for some, a shortened life span (Tucker et al., 2009).

Neurofibromatosis 1

The Nf1 gene is located on chromosome 17 and produces a protein product called neurofibromin (Gutmann, 2001). There can be many different mutations in the Nf1 gene that result in the condition, the majority of which result in a truncated protein product (Cnossen et al., 1998; Boulanger et al., 2005; Tucker et al., 2005). Nf1 acts through the ras cell-signaling pathway, and is considered a tumor suppressor gene, although the condition has many features in addition to tumors. Some of the more common clinical features associated with NF1 are café au lait spots, axillary and inguinal freckling, the development of neurofibromas, iris Lisch nodules (Tucker et al., 2009), bone disorders such as scoliosis, learning disabilities, and increased risk for cancers.

Plexiform Neurofibromas

Neurofibromas, the hallmark tumor of NF1, are benign peripheral nerve tumors that can be classified in several different forms. Cutaneous neurofibromas are small peripheral tumors that occur in the skin or subcutaneous tissues in more than 95% of patients with NF1 by adulthood. In distinction, plexiform neurofibromas (PNF) are typically larger, arise from one or
more major nerve roots and spread along multiple fascicles of the nerve, leading to a diffuse mass of thickened nerve fibers (Korf, 1999). PNFs are thought by many to be congenital lesions, can be seen in young children, and often demonstrate rapid growth in the first 5 years of life (Korf et al). These tumors vary greatly in growth rate, shape, and size (Korf, 1999) and are usually detected by clinical examination or MRI (Darrigo et al., 2007; Van Meerbeeck et al., 2009). Many of the PNFs located internally require MRI for detection. Studies with whole body MRI have shown internal PNFs in up to 56% of young adults with NF1 (Mautner et al, 2008). Although no standard of care is currently recognized, some clinicians have recommended that patients with NF1 have screening MRI’s every 1 to 5 years beginning at the age of 12 (Waggoner et al., 2007); however no screening recommendations for adults have been published. Screening of PNFs and follow-up widely varies between clinicians and patients, and there are currently no recommendations recognized for management of adults with PNFs. PNFs are of concern because of their ability to grow in areas that can cause pain, loss of function, and they have tendency for malignant transformation to malignant peripheral nerve sheath tumor (MPNST) (Mautner et al., 2008; Nguyen et al., 2011; Evans et al., 2002).

**Clinical Complications**

Depending on the location of the tumor, the patients may experience significant, even life threatening issues (Needle et al., 1997). For example, some plexiform neurofibromas will develop near the airway in the neck or face, and eventually will grow and constrict the patient’s airway. Another common location to cause morbidities are paraspinal PNFs, which can cause pain or spinal cord compression and subsequent weakness or paralysis. Additionally, PNFs located internally have been reported to cause severe bleeding problems, which can result in death. Unfortunately, surgery alone cannot always resolve these complications because some
PNFs typically quite difficult to remove in entirety; and those that can be removed often grow back rapidly and more aggressively than before (Waggoner et al., 2007; Nguyen et al., 2011).

A previous study conducted at Cincinnati Children’s (1997-2007) investigated PNFs in the pediatric population and the morbidities associated with these tumors. The study focused on tumor size, location, need for surgery, loss of function, treatment, mortality, and chemotherapy (Prada et. al 2011). The most common morbidities leading to need for surgery identified were neurologic loss of function, disfigurement, orthopedic pain or loss of function, and airway complaints. However, the study of morbidities in adult NF1 patients with PNF is limited. This is a problem because if morbidities are substantial then systematic screening may be warranted.

**Purpose**

Our study aimed to address the morbidities in the adult population with NF1 and PNFs to establish if they experience similar or different morbidities to the pediatric population. The purpose of this study was to characterize PNF locations, complications and identify factors associated with these morbidities in the patient population. We also specifically looked at development of malignancy, as MPNST is known to be both associated with PNF and a major cause of death in patients with NF1. Our study aimed to assess the rates of surgery in the adult population. We investigated three common morbidities (development of malignancy, need for surgery, and chronic pain) and looked at whether factors such as age and tumor location are associated with these morbidities.

Our study addressed the question; are there relationships between the different morbidities experienced by the adult patient population with Neurofibromatosis type 1 (NF1) who develop plexiform neurofibromas (PNF) and the patient characteristics? Specifically does a relationship
exist between: tumor location and need for surgery, and patient’s age and development of a malignancy (MPNST)?

1 Morbidities in this study are defined as chronic pain, need for surgery and development of a malignancy (MPNST) from the PNF.
Methods

Participants

Study subjects were patients with a clinical diagnosis of NF1 over the age of 18 as of 7/31/2013, and had a PNF. Subjects were identified from the adult patient population followed at Cincinnati Children’s Hospital in the NF1 clinic. All patients seen at Cincinnati Children’s Hospital NF1 clinic are entered into an electronic database, which tracks information about their age, disease progress, and appointments. The database was used to identify subjects by patient’s name and medical record number (MRN). The patients’ charts were then located in both paper and electronic format.

Inclusion criteria:

- Study subjects must have a clinical diagnosis of NF1
- Study subjects must have a clinically significant PNF. This can be defined as a PNF of >5cm, or a PNF that has already required surgery due to complications it was causing, or a PNF <5cm in an area where <5cm is determined to be of significant size. Areas where a PNF <5cm would be considered clinically significant are the head/neck region, genital region, and the pericardial sac. For this study PNFs were detected by clinical exam or MRI imaging, none of the study subjects had whole body MRI screening.
- Subjects must have been seen at Cincinnati Children’s NF clinic at least 2 times. Subjects must have a complete medical chart to be included in the study.
- If there were areas of the medical chart that were missing about surgery, tumor location, or age, charts were not included.
• Missing information allowed was race, ethnicity, and chronic pain. Pain was found to not be documented consistently, and race and ethnicity were self reported. Patients were given the option to report unknown, and were not excluded if this was reported.

For this study, a waiver of the Informed Consent Process and HIPAA authorization was obtained from the CCHMC IRB and The University of Cincinnati IRB.

Study Procedures

After receiving IRB approval, a case report form was used to collect data from the medical charts. Data was abstracted from the medical charts beginning 1/1/1990 through 7/31/2013. Data collected included patients MRN number, patient’s date of birth, surgery on PNFs, development or diagnosis of malignancy, pain (documentation and date of documentation), race (self-report), ethnicity (self-report), sex, and mortality (if present and date). Data were stored in REDCap, a HIPAA compliant database.

Definition of Study Variables

For this study, we used a case report form with the variables malignancy, mortality, and location defined a priori. Malignancy was defined as the development of an MPNST. Malignancy was determined based on a clinical diagnosis of an MPNST (diagnosis from a clinician, reports from imaging, and pathology reports of the tumor). Date of first occurrence was recorded to assure that only adult malignancies were accounted for in this study. Importantly, for this study only MPNSTs that were associated with previously documented PNFs were included in the same area. Mortality was defined as death due to a subject’s PNF. This can include complications associated with the PNF or malignancy. Location of PNF and MPNSTs were classified into five groups: extremities (arms/legs), paraspinal, head/neck, thoracic, and pelvic.
**Derived Variables**

Several variables were derived after the chart review. To document chronic pain, the physician’s note of each patient encounter was reviewed to determine if there was a report of the presence or absence of pain. Up to three reports of pain were documented along with the date of the encounter. Chronic pain was defined as the occurrence of two reports documenting the presence of pain at least 11 months apart. Age was calculated as the age at chart review unless the subject was deceased, then the age was taken as the age at death. Location was further reduced into core vs peripheral, such that core was considered pelvic, thoracic, and paraspinal whereas peripheral included extremities and head/neck.

**Data Analysis**

To characterize the adult NF patients with PNF, we described the population using frequency (categorical data), means ± standard deviation (for normally distributed continuous data), and medians (interquartile range) (for non-normally distributed continuous data). As individuals could have more than one location for PNF, surgeries, and MPNSTs, frequencies for locations was calculated separately for each location, thus the sum of locations exceeds 100%.

To identify factors associated with PNF surgery, we compared subjects who had surgery versus subjects who didn’t have surgery on the basis of number of PNFs, location of PNFs, and chronic pain. For number of PNFs, Wilcoxon rank sum was used given the skewed distribution of PNF. For location of PNF and chronic pain, we used 2x2 contingency tables unless cell counts fell below 5 at which point Fisher’s Exact test was used. All analyses were performed in JMP Genomics v5.0.
**Results**

*Characteristics of the Study Population*

A total of 69 subjects met inclusion criteria (Table 1). Overall, the majority of the participants were female (53.6%) and White (82.1%). The only ethnicity represented was Non-Hispanic. The average age of study participants was 32.0 (± 11.4) years (age range 18-71 years). The presence or absence of chronic pain could be documented in 35 subjects. The remaining subjects did not have pain consistently documented in the chart so it could not be assessed. Of those, 60% (n=21) were considered to have chronic pain, continuously documented within 11 months of each report.

*Plexiform Neurofibroma (PNF) Locations*

In the 69 subjects, 94 plexiform neurofibromas were documented, with 37.8% (26) having more than one PNF (median 1, interquartile range 1-2). The maximum number of PNF in any one subject was four. When examining the presence or absence of PNF at each location within subjects, extremities (42%) were the most common location for PNF followed by paraspinal (32%), head/neck (30%), thoracic (23%), and pelvic (9%) (Figure 1).

*Plexiform Neurofibroma Surgery*

The rate of surgeries on plexiform neurofibromas was 50.7% (n=35), and 12 patients reported more than 1 surgery (maximum 3). When examining the occurrence of surgery within these 35 individuals, surgery was most common in paraspinal 37.1%, followed by head/neck (31.4%), extremities (20%), thoracic (20%), and pelvic (5.7%) (Figure 1). Of note the frequency of surgeries for extremity PNFs was lower than the frequency of extremity PNF (p = 0.026).
Malignancies

There were seven participants that developed malignant peripheral nerve sheath tumors (Table 1). The average age of onset was 24.0 ± 5.1 years. Of the seven patients with MPNSTs six had a surgery on their MPNST. Most individuals had a single MPNST (median 1, IQR 1-2, range was 1-2). Two individuals developed two MPNSTs. The most common location for MPNSTs was pelvic and thoracic (both 43%) followed by paraspinal (29%) and head/neck (14%). There were no MPNSTS of the extremities in this patient group. The distributions of MPNSTs varied substantially from both overall PNFs and PNFs having surgery (Figure 1). MPNST treatment was categorized by surgery alone, chemotherapy alone, chemotherapy with surgery (both), or other (radiation or clinical trial). There were not any participants that received surgery alone as a form of treatment, but there was one participant that did receive chemotherapy alone. The majority received a combination of chemotherapy and surgery with 85.7% (n=6) and one patient received radiation. Four patients died of MPNST, and 3 were surviving at the time the study concluded.

Predictors of Surgery

Number of Plexiform Neurofibromas

To determine if the number of plexiform neurofibromas an individual had was associated with surgery, we compared the number of PNFs between those with and without surgery. Individual who underwent surgery had more PNFs (p = 0.02) but this difference was only apparent in the upper end of the distribution as those without surgery never had more than 2 PNFs whereas those with surgery ranged from 1 to 4 (Figure 2).
Chronic Pain

Pain was not consistently documented in the medical records reviewed, and we were only able to assess pain for 35 study subjects. There was no significant difference in rate of surgery between those with and without chronic pain. There was a slight trend that of those reporting chronic pain, patients with tumors in core locations (pelvic and thoracic), those with malignancies, and those who required surgeries were more likely to report chronic pain. There were no significant differences (p > 0.01).
Discussion

There is currently no standard of care for adult NF1 patients with PNF possibly due to the limited documentation of its natural history. In an effort to clarify the natural history of adult NF1 patients with PNF, we performed a retrospective chart review to quantify morbidity and mortality. Our results showed that our adult patients had substantial morbidity and mortality from their PNFs. Specifically, we found PNFs in all regions of the body with over 37% of our participants having more than one PNF. Importantly, there was a large burden with respect to surgery with over 50% of participants undergoing surgery for PNFs. Of those who underwent surgery, 17% had more than one surgery. Unfortunately both malignancy and death were common in our cohort. We found that extremities were the most common location for PNFs followed by paraspinal, head/neck and thoracic with few pelvic PNFs. These results are in contrast to a previous study of children in which head/neck (38%) was the most common location, followed by extremities (22%), and trunk (17%) (Prada et. al, 2011). However, Waggoner found that the majority of PNFs occurred in extremities and the trunk (Waggoner et. al, 2000). Both studies support our results that PNFs frequently occur in extremities and the trunk.

It is not surprising that a substantial number of patients had multiple PNFs. This follows the patterns reported in previous studies (Prada et. al, 2011; Waggoner et. al, 2000). Our results showed some differences in the number and pattern of PNF from those reported in studies using whole body MRI Imaging to screen for PNF tumor burden. Plotkin et. al (2011) found that tumors in the head/neck, thorax, and pelvic area were higher in patients over 40. Detection of tumors in these areas typically requires imaging since they cannot always be seen on a physical exam. Patients with tumors in these locations are not only at risk for requiring surgery in
adulthood, but are also at risk for serious complications from these tumors including bleeding (Mautner et. al, 2006). In our study, the majority of tumors were found in the extremities. This is may be attributed to the fact that PNFs in our patients were only identified on physical exam, or due to symptomatology.

The morbidities associated with PNFs observed in this study were pain, tumor burden requiring surgery (due to loss of function, disfigurement, overgrowth of tumor, etc.) and malignancy. Previous studies have also reported that these are common morbidities in this patient population. For example Kim et. al (2009) found that pediatric patients with NF1 who had enrolled in clinical trials for treatment of PNFs frequently had surgery (over 50%) and pain (38%).

_Surgery on Plexiform Neurofibromas_

One explanation for high rate of surgery could be continued growth of PNF in adulthood. As these tumors increase in size it is more and more likely that they will interfere with function or cause pain. On the other hand, we cannot exclude the possibility that the high surgery rates may in part be due to the fact that our adult NF1 patient population is biased with more serious medical problems, and that adults with NF1 but with fewer problems and are not seeking care. Nonetheless, there are a substantial number of patients identified who underwent surgery supporting the need for continuing care.

We found that the number of PNFs in a patient was associated with surgery. Indeed, all patients with three or more PNFs underwent surgery. One of the most common reasons patients have surgery is for elective/cosmetic reasons (Canavese et. al, 2011; Needle et. al, 1997). This is followed by dysfunction, diagnostic biopsy, pain, and malignancy (Nguyen et. al, 2013; Needle et. al, 1997). It stands to reason based on these results and the findings of our study that the
more total PNFs a patient has, the more likely they are to require surgery. With additional research in this area, number of PNFs as well as the size and location may be a good predictor for the likelihood of surgery in adulthood. Because the morbidities requiring surgery are so variable, adults need to be followed for progression of PNFs. This will allow changes over time to guide the management of existing PNFs.

When looking at location as a predictor of surgery, patients had the most surgery in the areas of the body that were near the trunk; thoracic, paraspinal, pelvic, and head/neck. Surgeries were significantly less likely to occur in individuals with a PNF in an extremity. There are not any current assessments of surgical outcomes based on location of PNF, but PNFs in the trunk and head/neck seem to have higher rates of morbidity (Prada et. al, 2011; Mautner et. al, 2008).

Both the adult and pediatric patients with NF1 have high rates of surgical intervention. A greater percentage of the adult population had surgery compared to pediatric patients. Additionally, pediatric patients who had surgery for PNFs were more likely to need a second surgery on the tumors within ten years (Prada et. al, 2011). It is therefore likely that they will need additional surgeries on their tumors into adulthood.

Malignancies

Locations of MPNSTs in study participants did not follow the same pattern of locations of PNFs. There were very few pelvic PNFs, yet pelvic MPNSTs occurred at one of the highest rates. Our results show that patients were significantly more likely to have MPNSTs in the areas of the body closest to the trunk (head/neck, pelvis, thoracic cavity, paraspinal). There is data that shows that several types of tumors occur at higher temperatures naturally in the body (Stefanadis et. al, 2001; DeNeve et. al, 1988). The PNFs in central locations would be exposed to
higher temperatures which could contribute to higher rates of malignancy.

Of note, our study did not include patients without PNFs, and therefore did not include patients with MPNST that arose independently of a PNF. Evans et. al (2002) found that 38% of the MPNSTs were in deep location and did not arise from preexisting PNFs. This study had limited numbers of MPNSTS. Additionally, it is very difficult to tell if an MPNST arose from a PNF unless the patient has been followed and their PNFs have been well documented. Assessment of patients with internal tumors through serial MRI may help determine who is most at risk for developing an MPNST by identifying changes prior to transformation and/or metastasis (Mautner, 2008).

**Pain**

A significant proportion of patients in this study reported having chronic pain. Based on the rates of surgery in our patients, pain could be a factor influencing those who underwent elective surgery. In previous studies, the majority of patients with MPNSTs report pain as a morbidity. Of interest, pain was not reported more frequently in MPNST patients. This should be interpreted with caution due to small sample size of MPNSTs and the retrospective nature of the study.

**Limitations**

One of the limitations to this study was that it was a retrospective chart review. We were not able to contact patients to fill in missing data when charts were incomplete. It was also difficult to track down some of the surgical reports and patients who did not have complete charts. Patients with missing information could not be included in this study, which limited our sample size.

Some of our sample sizes were small for tumor locations and for malignancies which
limits conclusions that can be. There is clearly a need for additional research to increase the understanding of PNFs in adults with NF1.

**Future Directions**

The major concerns that this study focused on were the need for surgery and development of malignancy. Current recommendations suggest that regular imaging is not necessary in adults. However, some tumors, such as paraspinal and pelvic can only be detected early on through imaging (Oates et. al, 2013; Tonsgard et. al, 1998). Several studies have reported that serial follow-up with MRI for an internal tumor is necessary to monitor for growth and signal changes (Nguyen et. al, 2011; Plotkin et. al, 2012; Rasmussen et. al, 2001). In addition, MPNSTs can often be detected through imaging, based on changes noted in the tumor. Early detection of MPNSTs is important as studies have shown that once an MPNST has become metastatic there is no effective way to treat it (Tucker et. al, 2005; Piliivaki et. al., 2003). Performing regular MRI on these patients may allow for earlier detection of MPNSTs. More information is necessary on how regular imaging impacts the adult patient population.

Recent preliminary clinical trials suggest that new drug therapies such as the class of MEK inhibitors may have some efficacy in shrinking PNFs. Availability of such agents could significantly change the approach to management of PNFs in adults, and could reduce the likelihood of surgery while reducing the risk of morbidities from tumor growth (Jessen et. al., 2013). Additional studies should be conducted to determine rates of surgery in these patients and the impact drug therapy can have on this morbidity. Morbidities in this patient population are difficult to assess through retrospectives studies. We noticed a trend in chronic pain, but it is difficult to accurately say how much this impacts patients without consistent assessment and documentation.
Conclusions

This study has investigated PNFs in adults with NF1. Interestingly, adults had more PNFs in extremities compared to any other location. However, adult patients are experiencing more morbidity with PNFs located in areas that are not the extremities. They experienced higher rates of surgery and MPNST development in the head/neck, thoracic, pelvic, and paraspinal areas. The more PNFs a patient has, the more likely they are to require surgery. Almost all mortality was due to MPNSTs. The exception was one participant who passed away from spontaneous bleeding into an internal PNF. Chronic pain was a serious problem in these patients. More research needs to be done to assess how severely this impacts quality of life for these patients. Future prospective studies are required to better understand this patient population and the impact that new therapies and regular imaging can have on preventing morbidity and mortality.
References


Tables and Figures

Tables

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<td>10.1 (7)</td>
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<td>7.2 (5)</td>
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<td>Chronic Pain**</td>
<td>60.0 (21)</td>
<td>56.5 (13)</td>
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Table 1. Characteristics of the Study Population
* Out of 66 with reported race/ethnicity
** Out of 35 patients
Figure 1: Distribution of PNF, Surgery Due to PNF, and MPNSTs.

Figure 1 shows the distribution of PNFs, rates of surgery, and rates of malignancy by location.
Figure 2: Comparison of Number of PNF by Surgery Group

Figure 2 shows rates of those subjects who did not have surgery and had surgery based on number of PNFs.
# Appendices

## Case Report Form

**Confidential**

### Demographics

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- Male
- Female
- Other
- American Indian/Alaska Native
- Asian
- Native Hawaiian or Other Pacific Islander
- Black or African American
- White
- More Than One Race
- Unknown / Not Reported
- Non Hispanic
- Hispanic
- Unknown
- Alive
- Deceased
- Consistently Employed
- Sporadically Employed
- Never Employed
- N/A
# PNF Tumor Information

## Clinical NF1 Diagnosis
- Listed in Chart twice
- From Outside record (based on Clinical Dx)

## Number of PNF

## PNF Location

### Location First PNF
- Head/Neck
- Thoracic
- Pelvic
- Paraspinal
- Extremities

### Size of 1st PNF

### Location of Second PNF
- Head/Neck
- Thoracic
- Pelvic
- Paraspinal
- Extremities

### Size of 2nd PNF

### Location of Third PNF
- Head/Neck
- Thoracic
- Pelvic
- Paraspinal
- Extremities

### Size 3rd PNF

### Location of Fourth PNF
- Head/Neck
- Thoracic
- Pelvic
- Paraspinal
- Extremities

### Size 4th PNF

### Location of Fifth PNF
- Head/Neck
- Thoracic
- Pelvic
- Paraspinal
- Extremities

### Size 5th PNF

### Date MRI

(This could be date of MRI or clinical description)
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# Chronic Pain

## Time Point 1

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## Time Point 3

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<tr>
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