



# Efficacy of Prednisone in Children with Acute Nonspecific Mesenteric Lymphadenitis: A Pilot Study

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## ABSTRACT

**Background:** Acute nonspecific mesenteric lymphadenitis (ANML) is a common cause of acute abdominal pain in children with no specific treatment. **Methods:** A total of 13 patients (6 boys, 7 girls) aged 7.3 (5–13.5) years with severe acute abdominal pain were evaluated using ultrasonography and laboratory tests to establish the diagnosis of ANML. They were treated with prednisone 1 mg/kg (max 40 mg daily) for a maximum of 5 days. The intensity of abdominal pain was evaluated before and after treatment using a numeric rating scale. **Results:** All patients had pain scores above 6/10 before, and below 4/10 after treatment with prednisone. Intensity of abdominal pain after treatment for 1–5 days decreased significantly ( $p < 0.001$ ), with no recurrence at follow-up within 3 months. All other pre-existing signs and symptoms, such as nausea, vomiting, anorexia, fever, diarrhea, and constipation were found to disappear with no adverse effects of corticosteroid therapy. **Conclusion:** These results suggest that the treatment with prednisone in selective patients with ANML can reduce the duration of abdominal pain.

## KEYWORDS

mesenteric lymphadenitis; corticosteroids; abdominal pain; children; lymphoma

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Received: 25 November 2020

Accepted: 22 April 2022

Published online: 29 June 2022

Acta Medica (Hradec Králové) 2022; 65(1): 25–28

<https://doi.org/10.14712/18059694.2022.12>

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## INTRODUCTION

Acute nonspecific mesenteric lymphadenitis (ANML) is a well-known and common cause of acute abdominal pain in children. The main symptom of ANML is abdominal pain, often of extreme severity, whereas other characteristic symptoms include fever, diarrhea, constipation, nausea, vomiting, and anorexia accompanied by normal or mild elevated markers of inflammatory conditions (1, 2).

ANML is a self-limiting disease with no specific treatment, and pain disappears within 2–3 weeks (3). The goal of the current pilot study was to evaluate the efficacy of oral prednisone for pain relief in children with ANML.

## MATERIAL AND METHODS

A total of 13 children with ANML in the Children's Ambulatory Care Centre were evaluated by the pediatric gastroenterologist (P.M.) between September 2018 and August 2020. Some patients included in this study were reported in detail elsewhere as a case report (4). This study has been performed according to the Declaration of Helsinki and the Research Ethics Board at Children's Ambulatory Care Centre who gave its approval on August 7, 2018 (number 1/08/2018). One of the patient's parents or legal guardian had to sign the consent form before the study inclusion. Only 3 patients with ANML were excluded from the study – one parent refused to sign the consent and another didn't apply the therapy after signing. The third patient was an 8-year-old boy who was not included in the study because the abdominal ultrasound showed thickening of the distal part of the ileum with enlarged, rounded lymph nodes at the mesenteric root scattered throughout the peripheral mesentery. During the examination, abdominal pain was minimal and the patient did not return although further investigations and controls were scheduled. About 23 days after the first occurrence of disturbances, the child's clinical condition worsened with acute onset of colicky pain, rectal bleeding, and signs of ileocolic intussusception. He was hospitalized and after the surgical intervention, histological evaluation of the resected distal segment of ileum and lymph nodes was interpreted as non-Hodgkin's lymphoma (NHL; Burkitt lymphoma subtype).

## PRETREATMENT EVALUATION

The diagnosis of ANML in children was made after observing the following conditions: (a) characteristic signs and symptoms; (b) an abdominal ultrasound demonstrating enlarged three or more lymph nodes and short-axis diameter of 8 mm or more in at least one of them; and (c) laboratory and ultrasound exclusion of appendicitis along with other causes of abdominal pain (5). The sonographer used a high-frequency linear transducer (6–13 MHz; Hitachi Medical Corporation, Japan). Ultrasonography performed by an expert sonographer (R.Z.) resulted in the following findings: size criteria of the nodes, the longitudinal diameter and the transverse diameter, and the ratio of the former to the latter calculated to obtain Solbiati index (6).

## TREATMENT AND ASSESSMENT OF SYMPTOMS

Patients were treated with a dose of oral prednisone 1 mg/kg (maximum 40 mg) once daily in the morning for 2–5 days. Parents were encouraged to sign consent forms, which stated the use of acetaminophen for analgesia. Patients subjectively evaluated the intensity of the pain using a numeric rating scale (NRS) with numbers ranging from 0 to 10 with 0 denoting “no pain” and 10 representing “worst possible pain” (7). It is notable that we only included patients with pain scores above 6/10 in the study. Pain scores below 4/10 were considered as a satisfactory therapeutic response. The last dose of prednisone was received by patients on the day after the NRS score was found to be below 4/10. There were telephonic reminders for completing the NRS every day, and patients were examined by the pediatric gastroenterologist every 2 days until complete pain relief. All children were encouraged to perform ultrasonography after 1 month. The questionnaire was administered by one of the authors during a clinic visit or a phone interview after 3 months.

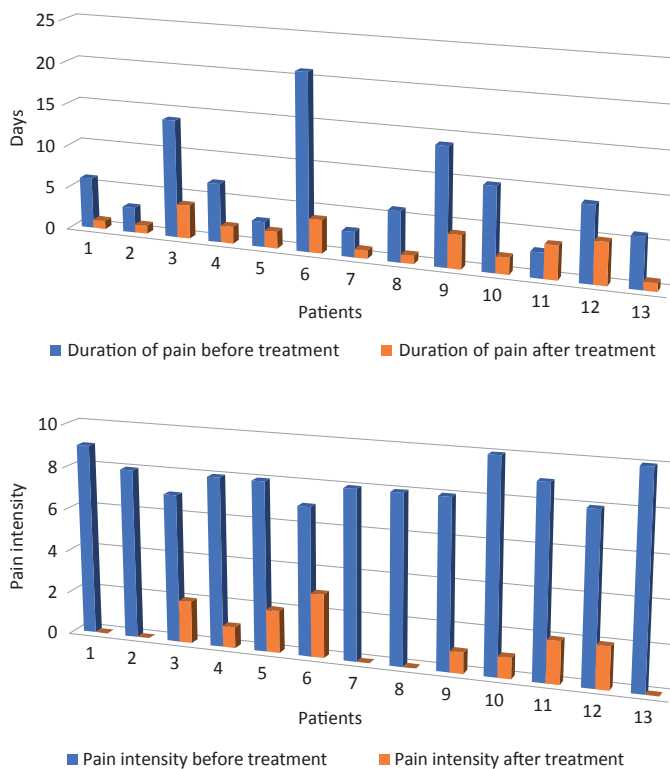
The effect of treatment on the intensity of the pain score was analyzed using Chi-square test. In addition, Pearson's correlation test was used to assess the correlation between the reduction of the initial pain and age of patients, duration of pain before treatment, and duration of pain after treatment. Differences were considered to be statistically significant when the p value was 0.05 or less.

## RESULTS

Of the 13 patients, 6 were boys and 7 were girls, the mean age of  $7.3 \pm 2.7$  years (age range, 5–13.5 years). All patients except one had other associated symptoms, such as vomiting (7 children), anorexia (5 children), fever (4 children),

**Tab. 1** Characteristics of 13 patients with acute nonspecific mesenteric lymphadenitis.

<b>Gender (M/F)</b>		7 : 6
<b>Age (y)</b>		7.3 (5–13.5)
<b>Location of pain (n)</b>	Periumbilical	5
	Ileocecal	4
	Ileocecal and periumbilical	4
<b>Time on onset of pain (n)</b>	Daily and nocturnal pain	9
	Only daily pain	4
<b>Physical examination findings (n)</b>	Ileocecal	5
	Paraumbilical	4
	Diffuse	3
	Epigastric	1
<b>Inflammatory markers (n)</b>	Rebound tenderness	3
	Leukocytosis ( $\geq 13.5 \times 10^9/L$ )	0
	C-reactive protein increased ( $\geq 5$ mg/L)	4



**Fig. 1** Pre- and post-treatment duration of pain and pain scores of 13 patients with acute nonspecific mesenteric lymphadenitis.

diarrhea (4 children), and constipation (1 child). One patient described a history of weight loss of 1 kg within 2 weeks. The clinical characteristics, presence of leukocytosis, and increased C-reactive protein are listed in Table 1.

Laboratory tests of the patients included amylase, liver function tests, lactate dehydrogenase (LDH), urea, creatinine, urinalysis and stool parasite analysis were normal in all patients. In 4 patients with diarrhea, the stool culture was negative.

Abdominal ultrasound showed enlarged lymph nodes in all children. Solbiati index was over 2 in all patients, and enlarged lymph nodes were noted only in the mesentery, with normal dimensions of the spleen and liver. The pre- and post-treatment pain duration, and scores are shown in Figure 1.

In patients with ANML who were treated with prednisone, pain scores decreased significantly at 1-5 days follow-up after the treatment ( $X^2 = 0.000$ ;  $p < 0.001$ ). The variable of years with the variable of decrease in initial pain (negative and significant  $R = -0.699$ ,  $p = 0.008$ ) indicates that with the increase of the first, the second variable will fall. The variable of the duration of pain before treatment with the variable of decrease in initial pain (negative and significant  $R = -0.588$ ,  $p = 0.035$ ) indicates that with the increase of the first, the second variable will fall. The variable of duration of pain after treatment with the variable of decrease in initial pain (negative and significant  $R = -0.699$ ,  $p = 0.008$ ) indicates that with the increase of the first, the second variable will fall.

In a 5-year-old girl, the pain disappeared after 3 days and thus the parents ceased the therapy. However, after

1 day without having any disturbances, on the 5th day, the pain intensity increased showing a 7/10 score and we had to continue with prednisone for 2 more days. After that period, the patients' NRS score was 2/10 and we discontinued the use of therapy with no recurrences. In 5 patients, the pain completely disappeared – 3 patients with a pain score of 1, 4 patients had a pain score of 2, and 1 patient had a pain score of 3.

All the other pre-existing signs and symptoms were found to disappear during corticosteroid therapy. A total of 6 patients were examined with control ultrasound 1 month after their inclusion in the study and their mesenteric lymph nodes were normal. After the follow-up period of 3 months, no recurrence of abdominal pain or other gastrointestinal disturbances were noted.

## DISCUSSION

Corticosteroids are among the most widely used adjuvant analgesics in the treatment of neuropathic pain, for the management of metastatic bone pain, and also reduce visceral pain (8). The reduction of edema in response to corticosteroid therapy results in the clinical improvement of pain. Additionally, corticosteroids influence the nociceptor activation by decreasing the level of pro-inflammatory cytokines and prostanooids in peripheral neurons, thereby reducing the pathological electrical activity and produce beneficial effects in pain relief (9).

Numerous questions are related to this issue. First, some consider ANML a nondisease that deserves only supportive care (10). However, after the removal of patients' and families' concerns about the illness, they undisputedly expect earlier pain relief so that they can return to normal life. Every day, nocturnal, intensive, long-term pain can be very frustrating and can lead to a negative impact on the patient's quality of life. The alleviation of the pain can be very slow, and symptoms can persist for 3-10 weeks in half of the patients (5). Prednisone might, therefore, present a useful clinical option to meet patients' needs.

Second, many differential diagnoses exist when we encounter patients with mesenteric lymph node enlargement. However, one of the most worrisome diseases for physicians and patients are malignancies, with NHL as the most common primary tumor of the small intestine (11). The effect of pretreatment of corticosteroids on lymphomas has not been fully clarified, but in some patients, they can delay or mask a final diagnosis (12). The terminal ileum is the most commonly reported location of NHL in children younger than 16 years old, because of the high concentration of lymph tissue in that region (13). This is the reason why children with NHL often present with urgent clinical signs of ileocolic intussusception and small bowel obstruction (14), as in our patient who underwent urgent surgical intervention. Otherwise, lymphoma may also present with non-urgent clinical signs as an occult large and single or multiple abdominal masses in the abdomen (15). Ultrasonography and cross-sectional imaging techniques show many characteristic manifestations of NHL, such as the rounded nodes; concurrent involvement of mesenteric, retroperitoneal, and pelvic lymph nodes; and

fusion of enlarged lymph nodes. The NHL mostly involves other abdominal organs, such as the spleen, liver, kidneys, and intestinal tract with circular thickening or dilation of the intestinal cavity (13, 16). Additionally, some laboratory test variables were reported to be useful in predicting malignant diseases. Up-regulation of LDH in malignancies ensures efficient glycolytic metabolism in cancer cells and reduced dependence on oxygen in anaerobic pathway (17). As the tumor's rapid doubling time increases serum LDH, it represents a very valuable enzyme in the evaluation of disease extension (18). Akinci et al. concluded that in adult patients presenting with lymphadenopathy, such results as anemia, leukopenia, thrombocytopenia, high LDH levels, and the presence of splenomegaly, the Solbiati index score below 2 can be used to accurately predict malignant etiology (19). In our patients with ANML, we do not have any of those signs. Although during the diagnostic process a fairly broad list of potential diagnoses can be accurately excluded, and it seems reasonable to repeat sonography after 4–6 weeks.

This pilot study summarizes a subjective experience of pain and is not a placebo-controlled, double-blinded study. However, we believe it was still a valid observation because patients had a fairly good response to the treatment with prednisone and didn't have a recurrence of ANML.

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