Clinical And Laboratory Characteristics And Growth Outcomes Of Children With Growing Pains

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Research article

Keywords: growth, leg pain, growing pains

Posted Date: July 30th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-49622/v1

Abstract

Background: Growing pains is a benign, non-inflammatory pain syndrome of childhood, characterized by bilateral recurrent leg pain. Studies regarding the clinical and laboratory profile of growing pains are limited, especially in East Asia. The aim of this study was to analyze the clinical features, laboratory findings, and follow-up of children with growing pains.

Methods: Patients under 18 years of age with growing pains in National Taiwan University Children's Hospital between April 2006 and April 2019 were enrolled. Clinical features, laboratory data and medication records were analyzed. Changes of body height and weight before and after the symptoms were assessed by the paired samples t-test.

Results: After excluding 31 children with musculoskeletal diseases, 276 patients with a final diagnosis of growing pains were included, comprising 152 boys (55%) and 124 girls (45%). The mean age was 4.9 ± 2.7 years. Bilateral and lower limbs pain were present in 232 (84%) and all cases, respectively. There were 6 out of 16 patients (38%) with elevated alkaline phosphatase, and 3 out of 50 (6%) with positive antinuclear antibodies in low titers. There were no significant changes in body height and weight percentiles or z-scores at 0.5, 1, and 2 years after diagnosis, compared with baseline values. Symptomatic treatments were used in 33% of patients.

Conclusions: Growing pains is a common benign leg pain syndrome in children. Alkaline phosphatase elevation is commonly detected. It is not associated with rapid changes of body height and weight within 2 years of experiencing growing pains.

Background

Growing pains is a benign, non-inflammatory pain syndrome of childhood. There are no standardized and universally accepted diagnostic criteria for growing pains, and the diagnosis is often made by exclusion in clinical practice. The proposed combined diagnostic criteria for growing pains by Walters et al. described the key clinical features: (1) usually pain in both legs; (2) pain starts between ages 3 and 12 years; (3) pain typically occurs at the end of the day or during the night; (4) no limitation of activity nor limping; (5) the typical distribution in the anterior thigh, calf, and posterior knee muscles; (6) intermittent pain with some pain-free days and nights; (7) normal physical examination, no evidence of orthopedic disorders, trauma, or infections; (8) normal laboratory tests (such as erythrocyte sedimentation rate), radiograph and bone scan; (9) pain for at least 3 months; and (10) no associated lack of well-being [1].

Growing pains is the most common cause of musculoskeletal pain in early childhood. Previous studies showed a wide range of estimated prevalence from 2.6–49.4% due to different definitions of growing pains, poor population sampling, and disparate age ranges [2–6]. Growing pains is prevalent in children aged 4 to 6 years [4]. The etiology and pathophysiology of growing pains, though widely investigated, are still unknown. Laboratory tests usually yield normal results [7], although studies of the biomarkers for growing pains are very few. The prognosis is good as growing pains is self-limiting, and most of the

symptoms resolve by adolescence [8]. In the current study, we analyzed the clinical features, laboratory findings, and outcomes of Taiwanese children with growing pains.

Methods

This study was conducted retrospectively at National Taiwan University Children's Hospital, a large medical center. Patients less than 18 years old who presented with intermittent leg pain from April 2006 to April 2019 were enrolled based on the proposed diagnostic criteria of growing pains [1]. The exclusion criteria were symptoms and signs of arthritis (erythema, swelling, warmth, and/or tenderness in the joints), limping gait or limitation of activity, abnormal radiograph findings, abnormal inflammatory markers (such as C-reactive protein or erythrocyte sedimentation rate), or any systemic disease. Clinical features and medication records were analyzed. Laboratory data were collected and analyzed. This study was approved by National Taiwan University's Hospital Research Ethics Committee (IRB approval number: 201710060RINC). Informed consent was waived, as it was a retrospective study.

Body weight (BW), body height (BH), and body mass index (BMI) were collected from every patient's medical record at every visit. Each value was transformed to the percentile and z-score based on the growth curves of the WHO and Taiwanese Child Growth Standards [9–11]. Z-score is a score indicating how many standard deviations an observation is from a population median, adjusted for age and gender. To test the association between growing pains and BH or BW, we compared the baseline BH or BW with BH or BW at one year before diagnosis, and 6 months, 1 year and 2 years after diagnosis of growing pains, respectively.

Data analysis was conducted using SPSS statistics for Windows (version 22.0). Z-scores for BH, BW and BMI were calculated using a macro for SPSS obtained from the WHO website [12]. Independent samples t-test was used to compare continuous variables. Fisher's exact test was used for categorical variables. Paired samples t-test was used to compare percentiles and z-scores assessed at two different times. The figures were generated by GraphPad Prism (version 7.0). A P-value < 0.05 was considered significant.

Results

There were 307 patients with intermittent leg pain eligible for our study. After excluding 31 patients with other musculoskeletal diagnoses, 276 patients were analyzed. The excluded patients consisted of the following final diagnoses: 7 with pronated foot, 7 with flat foot, 5 with developmental dysplasia of the hip, 1 with tibia fracture, 1 with genu valgum, and 6 with arthritis, including 3 with juvenile idiopathic arthritis, 1 with IgA vasculitis, and 4 with unclassified autoimmune disease (Supplementary Fig. 1, Additional file 1).

The age of patients with growing pains was 4.9 ± 2.7 years (mean ± standard deviation) with slight male predominance (55%). For clinical presentation, 232 patients (84%) had bilateral leg pain and all (100%) had pain in the lower extremities. Symptomatic treatments were used in 90 patients (33%), including 35

patients (13%) treated with only oral analgesics, 52 patients (19%) treated with only topical analgesics and 3 patients (1%) received both treatments (Table 1).

Table 1
Demographic and clinical characteristics of children with growing pains

	N (%) or values
Total numbers of patients	276 (100)
Male	152 (55)
Age, years	4.93 ± 2.69 (1.17–16.92)
Body weight, kg	18.98 ± 9.36 (9.5–74.0)
Body height, cm	106.55 ± 18.08 (80.0-175.0)
BMI, kg/m^2	16.39 ± 4.17 (13.2–25.5)
Clinical presentation	
Bilateral pain	232 (84)
Onset of pain	
Morning	7/169 (4)
Afternoon	5/169 (3)
Night	157/169 (93)
Location of pain	
Upper limbs	12 (4)
Lower limbs	276 (100)
Limitation of activity	0 (0)
Examination	
Plain film	71 (26)
Laboratory tests	73 (26)
Management	
Observation only	186 (67)
Oral medication only	35 (13)
Topical medication only	52 (19)
Both oral and topical	3 (1)

BMI body mass index

* The values are expressed as mean ± standard deviation (range).

	N (%) or values
Follow-up	70 (25)
BMI body mass index	
* The values are expressed as mean ± standard deviation (range).	

For diagnostic tests, plain radiographs were performed in 26% of patients. Laboratory tests were also performed in 26% of patients. Elevated alkaline phosphatase (ALP) levels were found in 6 out of 16 patients (38%), and none had elevation above 1.5 times the upper limit of the normal range (Table 2). Patients with elevated serum ALP levels had significantly higher levels of lactate dehydrogenase (LDH) (Table 3). The mild elevation of white blood cell count and aspartate aminotransferase (AST) levels decreased to normal levels after 3–4 months of follow-up. There were 3 patients (6%) with abnormal antinuclear antibodies titers, one of which was 1:1280, and the titers became 1:80 after 4-month follow-up.

Table 2
Laboratory features in patients with growing pains

Parameter	Number, n	Mean value*	Elevated, n(%)	Abnormal elevated#, n(%)
WBC (k/uL)	71	8.33 ± 2.34	3 (4)	0 (0)
Hemoglobin (g/dL)	70	12.90 ± .0.91	7 (10)	0 (0)
Platelet (k/uL)	70	336.89 ± 83.83	6 (9)	0 (0)
CRP (mg/dL)	54	0.10 ± 0.23	0 (0)	0 (0)
ESR (mm/hr)	46	7.80 ± 4.27	0 (0)	0 (0)
LDH (U/L)	46	393.70 ± 210.07	7 (14)	2 (4)
AST (U/L)	26	32.38 ± 9.52	4 (14)	0 (0)
ALT (U/L)	22	13.32 ± 4.80	0 (0)	0 (0)
CK (U/L)	19	107.89 ± 29.88	0 (0)	0 (0)
ALP (U/L)	16	308.31 ± 159.76	6 (38)	0 (0)
C3 (mg/dL)	50	114.18 ± 19.96	0 (0)	0 (0)
C4 (mg/dL)	50	20.85 ± 7.77	0 (0)	0 (0)
ANA	50		3 (6)	3 (6)
RF (IU/mL)	25	All negative		
HLA-B27	5	All negative		

WBC white blood count, CRP C-reactive protein, ESR erythrocyte sedimentation, LDH lactate dehydrogenase, AST aspartate aminotransferase, ALT alanine aminotransferase, CK creatine kinase, ALP alkaline phosphatase, ANA antinuclear antibody (in titer, normal range is defined as titer less than 1:40), RF rheumatoid factor, HLA-B27 human leukocyte antigen B27

* The values are expressed as mean ± standard deviation

The values are higher than 1.5 fold of upper limits of the normal range, adjusted by age

Table 3
Comparison of clinical and laboratory features between patients with normal and elevated alkaline phosphatase levels

	N (%) or values*		p value
	Normal ALP (N = 10)	High ALP (N = 6)	
Male	6 (60)	1 (17)	0.145
Age (years)	5.60 ± 3.169	5.67 ± 2.422	0.965
Clinical presentation			
Bilateral pain	9 (90)	5 (83)	
Onset of pain			
Morning	0 (0)	0 (0)	
Afternoon	1 (10)	0 (0)	
Night	9 (90)	6 (100)	
Symptomatic treatment	3 (30)	0 (0)	
Follow-up	6 (60)	4 (67)	
Laboratory data			
WBC (k/uL)	8.86 ± 3.05 (N = 9)	7.06 ± 1.82 (N = 6)	0.219
Hemoglobin (g/dL)	12.91 ± 0.90 (N = 9)	13.60 ± 1.05 (N = 6)	0.197
Platelet (k/uL)	372.00 ± 107.52 (N = 9)	348.00 ± 97.05 (N = 6)	0.668
CRP (mg/dL)	0.04 ± 0.03 (N = 7)	0.05 ± 0.04 (N = 5)	0.594
ESR (mm/hr)	9.33 ± 5.13 (N = 6)	12.00 ± 2.83 (N = 2)	0.415
AST (U/L)	27.00 ± 5.35 (N = 7)	32.50 ± 0.71(N = 2)	0.210
ALT (U/L)	12.67 ± 3.39 (N = 6)	14.00 ± 1.41(N = 2)	0.471
CK (U/L)	80.00 (N = 1)	135.00 (N = 1)	
ALP (U/L)	197.60 ± 32.77 (N = 10)	492.83 ± 96.27 (N = 6)	
C3 (mg/dL)	113.73 ± 19.26 (N = 6)	126.20 ± 15.50(N = 5)	0.274
C4 (mg/dL)	19.85 ± 5.93 (N = 6)	26.96 ± 11.03 (N = 5)	0.204

WBC white blood count, CRP C-reactive protein, ESR erythrocyte sedimentation rate, AST aspartate aminotransferase, ALT alanine aminotransferase, CK creatine kinase, ALP alkaline phosphatase, LDH lactate dehydrogenase

* The values are expressed as mean ± standard deviation

	N (%) or values*		p value
LDH (U/L)	233.33 ± 34.86 (N = 9)	549.40 ± 116.64 (N = 5)	**0.003**
N of elevated LDH	0 (0)	3 (60)	

WBC white blood count, CRP C-reactive protein, ESR erythrocyte sedimentation rate, AST aspartate aminotransferase, ALT alanine aminotransferase, CK creatine kinase, ALP alkaline phosphatase, LDH lactate dehydrogenase

* The values are expressed as mean ± standard deviation

All patients recovered without significant long-term disabilities or co-morbidities. The distribution of body height z-scores at different time intervals from diagnosis is shown in Fig. 1. Compared to baseline BH, BW, and BMI, there were no significant changes in percentiles or z-scores at 1 year before, and 6 months, 1 year, and 2 years after the diagnosis of growing pains (Table 4 and Supplementary Fig. 2, Additional file 1).

Table 4
Body size parameters at different time intervals from diagnosis of growing pains*

	Time interval#				
	-1 (n = 30)	0 (n = 116)	0.5 (n = 15)	1 (n = 17)	2 (n = 17)
BH	100.41 ± 10.99	105.01 ± 12.79	105.40 ± 11.70	107.01 ± 7.49	118.82 ± 13.03
in cm	38.54 ± 26.38	42.67 ± 31.02	40.70 ± 31.80	36.93 ± 29.06	53.05 ± 29.74
in percentile	-0.35 ± 0.91	-0.22 ± 1.18	-0.30 ± 1.05	-0.42 ± 0.96	0.04 ± 1.01
z-score					
BW	15.69 ± 3.05	17.25 ± 4.66	16.92 ± 3.84	17.82 ± 2.33	22.81 ± 7.07
in kg	46.23 ± 27.97	45.13 ± 28.84	38.40 ± 21.40	45.14 ± 31.69	52.14 ± 32.72
in percentile	-0.19 ± 1.09	-0.16 ± 1.05	-0.33 ± 0.61	-0.17 ± 1.07	0.03 ± 1.10
z-score					
BMI	15.68 ± 1.86	15.50 ± 1.89	15.03 ± 0.75	15.56 ± 1.50	15.80 ± 2.34
in kg/m^2	55.02 ± 30.35	47.33 ± 31.48	43.55 ± 21.47	52.73 ± 27.51	50.05 ± 36.28
in percentile	0.10 ± 1.38	-0.05 ± 1.34	-0.22 ± 0.68	0.13 ± 1.08	-0.02 ± 1.37
z-score					

BH body height, BW body weight, BMI body mass index

* The values are expressed as mean ± standard deviation

The time interval is defined as the time elapsed between diagnosis of growing pains and record of body height, weight and BMI at another visit, with 0 being the point at which growing pains was diagnosed. Patients with negative elapsed time had records of body height, weight and BMI before they were diagnosed as having growing pains. None of the comparison between the time of diagnosis and other time points had statistically significant difference.

Discussion

We demonstrated the clinical features of growing pains in Taiwanese children with mean age at diagnosis of 4.9 years and slight male predominance. For diagnostic tests, plain radiographs and laboratory tests were performed in 26% of the patients. Only 14% of our patients needed oral medication for pain relief. We found that serum levels of ALP and LDH were elevated in 38% and 14% patients with growing pains, respectively. In an observational study by Qamar et al., elevated ALP was found in 38%

patients of growing pains, of whom 97.3% had vitamin D deficiency [13]. However, the association between serum ALP levels and growing pains was not significant in two previous studies [7, 14]. Signaling pathways including Wnt/β-catenin/TCF, BMP2/Smad/RUNX2, IGF/PI3K/RUNX2, and FGF/MAPK/ERK have been reported to induce ALP expression and bone mineralization. ALP expression is also restricted and regulated by $1,25(OH)_2$-vitamin D, retinoic acid, and parathyroid hormone [15]. Hypovitaminosis D reduces calcium absorption and serum calcium levels, triggering secondary hyperparathyroidism which subsequently increases bone resorption and serum ALP level [16]. Although ALP levels are thought to be elevated in children's rapid growth phase, our data showed that growing pains is not associated with rapid growth of body height and weight within 2 years of onset of symptoms [7].

In growing pains, whether there is a causal relationship with hypovitaminosis D or whether hypovitaminosis D is a risk factor for severe pain through peripheral and central mechanisms is unclear. Growing pains could be an early manifestation of histological changes in bone matrix associated with hypovitaminosis D [13]. In addition, vitamin D interacts with the nuclear receptors in the muscle tissues to increase muscle strength. Vitamin D deficiency is associated with chronic muscular pain or fibromyalgia in adults [17]. Women with chronic musculoskeletal pain and hypovitaminosis D had significant higher pain scores, compared with patients with normal vitamin D levels [18].

High prevalence (57–94%) of hypovitaminosis D was found among the children with growing pains in comparison with population prevalence [19]. Oral vitamin D supplementation has been shown to be effective in increasing serum vitamin D levels and reducing pain severity in children with growing pains, although there were no control groups for comparison in these studies [19–22]. However, children with growing pains with high BMI and elevated serum ALP levels showed less benefit from vitamin D therapy than those with lower BMI and normal ALP levels [19]. Half of our patients with high ALP levels had elevated levels of LDH at diagnosis. Those patients with elevated ALP and LDH levels might have mild inflammation that may cause musculoskeletal pain.

According to a population-based cohort study, vitamin D deficiency defined as a 25(OH)-vitamin D level < 20 ng/mL (50 nmol/l) and vitamin D insufficiency defined as a 25(OH)-vitamin D level of 21–29 ng/mL (52.5–72.5 nmol/l) were observed in 51% and 90.3% of Taiwanese children aged 5 to 18 years [23]. Since low serum 25(OH)-vitamin D levels are common in Taiwanese children, we recommend monitoring serum vitamin D and ALP levels at diagnosis and during follow-up and providing vitamin D supplements for children with growing pains and vitamin D insufficiency/deficiency.

The major limitation of the study was that we did not check serum vitamin D levels at disease diagnosis; this could not be overcome due to the retrospective study design. Another study limitation was the lack of healthy controls for the comparison of biomarkers, BW and BH. We used age-adjusted normal ranges of laboratory data and growth charts in percentile and z-score instead. Further large-scale prospective studies to investigate the association between vitamin D levels, serum ALP levels, the severity of growing pains, and lifestyle are warranted. It is possible that vitamin D deficiency or insufficiency may be

associated with growing pains, and hypovitaminosis D could develop secondarily, as a result of lifestyle, limited outdoor activities, or poor eating habits.

There are several other proposed hypotheses for growing pains, including anatomical factors such as flat feet, over-pronated feet, and joint hypermobility [24–28], lower pain threshold [29, 30], lower skeletal vascular perfusion [24, 31], reduced bone strength [32, 33], and psychological factors [34–36]. Various factors, individually or in association, might be responsible for the onset of growing pains. In our study, we excluded 31 patients with musculoskeletal diagnoses, including 21 children with over-pronated feet, flat feet, developmental dysplasia of the hip, and genu valgum. Careful evaluation by orthopedic surgeons for anatomical abnormalities in children with aching legs is important [37]. In a study by Lee et al., over-pronated feet accounts for 75% of pediatric patients with growing pains, and pain episodes were significantly reduced using foot orthoses [27].

Conclusions

In conclusion, growing pains is a common leg pain syndrome in children. There was no relationship found between growing pains and rapid growth within 2 years of diagnosis. ALP might be one of the potential biomarkers associated with the disease. However, more studies are needed to be clarified.

List Of Abbreviations

ALP Alkaline phosphatase

ALT Alanine aminotransferase

ANA Antinuclear antibody

AST Aspartate aminotransferase

BH Body height

BMI Body mass index

BW Body weight

CK Creatine kinase

CRP C-reactive protein

ESR Erythrocyte sedimentation rate

HLA Human leukocyte antigen

LDH Lactate dehydrogenase

RF Rheumatoid factor

WBC White blood count

Declarations

Ethics approval and consent to participate

This study was approved by National Taiwan University's Hospital Research Ethics Committee (IRB approval number: 201710060RINC).

Consent for publication

Not applicable.

Data sharing statement

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the National Taiwan University Hospital (109-A152). The National Taiwan University Hospital did not have a role in deciding the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication

Authors' contributions

CYL designed the project, collected and analyzed the data, and drafted the manuscript. HHY conceived and designed the project, collected the data, drafted and revised the manuscript, and approved the final manuscript for submission. JHL, LCW, YTL, WKW, and YHY designed the project and collected the data. BLC conceived and designed the project, and revised the manuscript. All authors have read and approved the manuscript.

Acknowledgements

Not applicable.

Authors' information (optional)

Not applicable.

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Figures

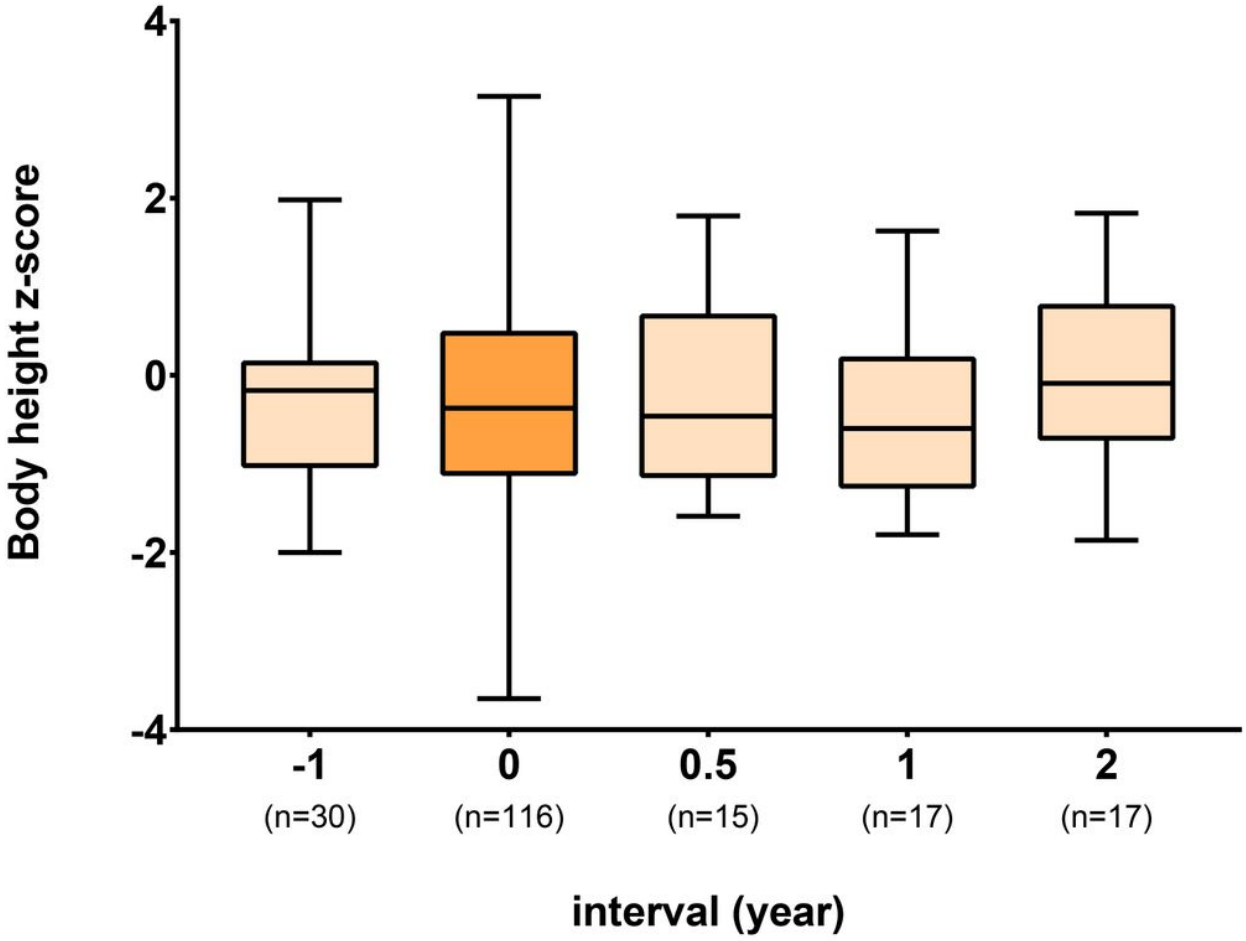

Figure 1

Box and whisker plots of body height z-scores at different time intervals from diagnosis. The time interval is defined as the time elapsed between diagnosis of growing pains and record of body height at another

visit, with 0 being the point at which growing pains was diagnosed. Patients with negative elapsed time had records before they were diagnosed with growing pains.

Supplementary Files

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- Additionalfiles.docx
- Additionalfile1.pdf