

# Role of Biochemical Markers in Diagnosis of Growing Pains

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### ABSTRACT

Growing pains (GP) are the most common form of nonspecific, recurrent leg pain syndrome in early childhood and frequent cause of paediatric outpatient visits. A case-control study was conducted at National Centre for Control of Rheumatic Fever and Heart Diseases, Dhaka, Bangladesh, from August 2021 to October 2022 to determine the relevant laboratory tests that can help diagnose growing pains among children reported hospital outpatient departments (OPD) with typical limb pains. 220 children (aged between 3 and 12 years) with non-specific musculoskeletal pain in limbs suspected of growing pains were enrolled. The controls were 200 clinically healthy children with no history of limb pain. Laboratory tests included complete blood count (CBC) with ESR, serum CRP, total calcium, phosphate, alkaline phosphatase, and rheumatoid factor. The mean age of children with growing pains was  $7.88 \pm 3.2$  years and boys were predominant (52.17%). Children with growing pains had marginally lower mean level of calcium ( $9.37 \pm 0.91$  mg/dl vs.  $9.52 \pm 0.93$  mg/dl) and phosphorus ( $3.58 \pm 1.18$  mg/dl vs.  $3.70 \pm 1.17$  mg/dl) than the controls. There were non-significant higher mean levels of CRP ( $2.64 \pm 1.03$  mg/dl vs.  $2.52 \pm 1.43$  mg/dl) and alkaline phosphatase ( $336 \pm 161$  U/L vs.  $313 \pm 153$  U/L) among GP children. Other parameters were within normal range according to age and sex. There were no significant differences between the results of those two groups. Therefore, we conclude that growing pains should be a clinical diagnosis. If inclusion and exclusion criteria are followed carefully, in children with limb pain typical for GP, there is no need for laboratory tests to make the diagnosis.

**Keywords:** Growing pains, children, biochemical markers, clinical diagnosis

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### INTRODUCTION

Growing pains (GP) are the most common episodic musculoskeletal pain during childhood<sup>1</sup>. Medical science still cannot fully explain the exact causes of this discomfort experienced by up to one-third of children at some period of childhood<sup>2</sup>. Some new terms like 'benign nocturnal limb pains of childhood' and 'recurrent limb pains of childhood' have also been used for such conditions<sup>3</sup>. The prevalence of growing pains worldwide in children aged four to six years is 37%, and in Bangladesh, the prevalence is 19% among school-going children<sup>4,5</sup>.

Growing pains are benign and usually resolve by adolescence<sup>6</sup>. They are typically non-articular, intermittent, bilateral and not associated with limited mobility. Physical examination does not reveal any objective signs of inflammation, and laboratory test results are generally normal<sup>7</sup>. The etiology of GP and

optimal treatment protocol remain unknown; currently, the diagnosis is based only on typical clinical symptoms and exclusion criteria. Several theories have been postulated to explain the etiology of GP; however, none of them has been established. The theories include muscular fatigue (an overuse response), emotional or psychological distress, a lower pain threshold, decreased bone strength, altered vascular perfusion, and joint hypermobility<sup>8</sup>.

In children with GP, biochemical markers in laboratory tests usually are found to be normal<sup>7</sup>. However, some studies linked dietary minerals and homeostasis of serum minerals to GP, especially vitamin D and serum calcium and phosphorus<sup>9-11</sup>. In the past GP was mentioned as a manifestation of calcium deficiency. A study in Bangladesh found that dietary calcium intake was relatively low in GP patients with lower bone strength<sup>12</sup>. Altered bone metabolism may occur in children with GP. Serum calcium and phosphorus are often considered as a reflection of bone homeostasis. Supplementation of calcium increases bone strength density and may resolve growing pains<sup>10,11</sup>. Hypocalcemia and hypophosphatemia are reported among children with GP<sup>9</sup>. Serum calcium, 25-hydroxyvitamin D, and phosphorus levels are the primary indicators of calcium and phosphorus metabolism in the body and may be considered independent diagnostic factors for growing pains<sup>13</sup>.

Although growing pains are benign and self-limiting, several reviews have recommended screening laboratory tests in children with GP and normal results of tests were reassuring to the family of the child<sup>7,14</sup>. In Bangladesh, growing pains is quite common among paediatric population. 75% of the patients with nonspecific pain in a specialized center were diagnosed clinically as having growing pains<sup>15</sup>. Therefore, this study was conducted to determine the role of relevant laboratory investigations especially serum calcium and several other biochemical markers in diagnosis growing pains in children with typical limb pains.

## METHODS

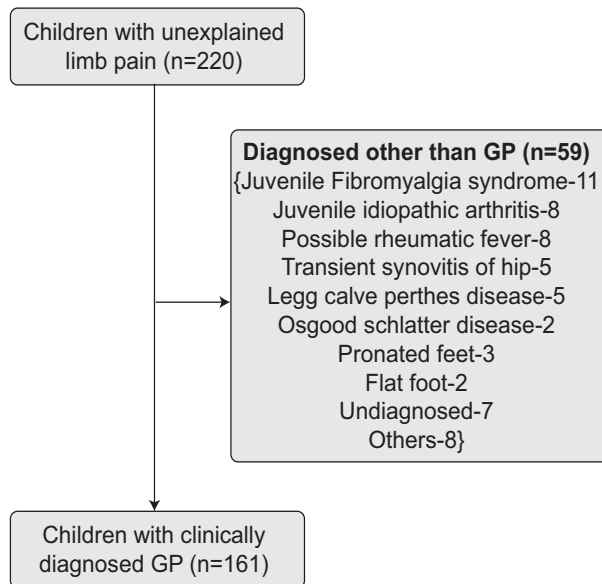
This case-control study was conducted at National Centre for Control of Rheumatic Fever and Heart Diseases (NCCRF&HD), Dhaka, Bangladesh, from August 2021 to October 2022. Children with unexplained limb pain suspected of growing pains attending the outpatient department were enrolled in the study as cases. The controls were clinically

healthy children with no history of past or current limb pain attending normal health visits or vaccination in the same period of time. Regarding the sex distribution, the cases and control groups had nearly equal proportions (200 control – 108 boys and 92 girls).

Suspicion of growing pains was based on the definition of growing pains and modified after Peterson<sup>16,17</sup>. Children with intermittent, non-articular limb pain occurring late in the day or at night were included as study population, whereas children with persistent pain, unilateral, increasingly intense pain at night which is still present the following morning and joint pain, having organic causes of pain or signs of inflammation such as local tenderness or swelling, underlying illnesses such as rickets, rheumatologic disorders, celiac disease and children with Vitamin D or minerals supplementation were not included in the study. Purposive sampling was used for selection of the samples. Clinical history, detailed and thorough physical examinations of the different systems and necessary laboratory investigations and radiological tests were carried out to diagnose growing pains by the specialists. Children of both groups underwent several laboratory investigations- complete blood count (CBC) with erythrocyte sedimentation rate (ESR) and serum levels of C-reactive protein (CRP), total calcium, phosphate, alkaline phosphatase (ALP), rheumatoid factor (RF). CBC was done in automated cell counter machine (ERBA Lyse, Germany) and biochemical tests were done in an automated analyzer machine (ERBA Automated XL-200). Tests were performed and normal reference ranges were included according to the manufacturers' instructions.

Information was collected from all the children using a preformed data collection form. All information regarding clinical features was recorded and relevant data were compiled on a master chart. Statistical analysis was performed using Microsoft Excel 2003 program. Student's t-test was done for testing statistical significance and  $p < 0.05$  was accepted as significant.

This study was approved by the Ethical Review Committee of National Centre for Control of Rheumatic Fever and Heart Diseases (NCCRF&HD), Dhaka, Bangladesh. Informed written consent was taken from parents or authorized legal guardian of each children. Besides, patient's (as children) assent was taken. Anonymity of patients and confidentiality of data was maintained strictly.



**Fig. 1:** Flowchart of enrollment of the study population (cases)

## RESULTS

A total of 161 children with clinically diagnosed growing pains and 200 healthy controls were

included. Mean age of children with growing pains was  $7.88 \pm 3.2$  years. Maximum 54(33.54%) of children were in 5-6 years age-group, followed by 44(27.33%) in 7-8 years age-group. Among the children with growing pains, boys were predominant and boy-girl ratio was 1.22:1 (Table-I). Comparison of results of laboratory investigations between children with growing pains and healthy control group are presented in Table-II. Average BMI was  $15.70 \pm 2.04$  and  $16.01 \pm 1.62$  in children with GP and control group respectively. Mean ESR was  $12.58 \pm 5.08$  mm among children with GP while in control group it was  $13.23 \pm 5.51$  mm and CRP was  $2.64 \pm 1.03$  mg/dl in children with GP but  $2.52 \pm 1.43$  mg/dl in the control group. Serum calcium and phosphorus level was  $9.37 \pm 0.91$  mg/dl and  $3.58 \pm 1.18$  mg/dl among children with GP whereas in healthy control it was  $9.52 \pm 0.93$  mg/dl and  $3.70 \pm 1.17$  mg/dl. The mean value of serum ALP among GP children was  $336.9 \pm 161$  U/L and  $313.0 \pm 153$  U/L in control group. RF was negative ( $<16$  IU/ml) in all GP children. Differences between the mean values of laboratory tests between children with GP and the control were not statistically significant ( $p > 0.05$ ).

**Table-I:** Age and sex distribution in children with growing pains (n=161)

Variables	3-4 years n(%)	5-6 years n(%)	7-8 years n(%)	9-10 years n(%)	11-12 years n(%)	Total n(%)
Boys	11(6.83)	28(17.39)	24(14.91)	14(8.69)	7(4.35)	84(52.17)
Girls	8(4.97)	26(16.15)	20(12.42)	15(9.32)	8 (4.97)	77(47.83)
Total	19(11.80)	54(33.54)	44(27.33)	29(18.01)	15(9.32)	161(100)

**Table-II:** Anthropometric and biochemical parameters in children with growing pains and healthy control group

Variables	Children with GP (mean $\pm$ SD)	Healthy Control (mean $\pm$ SD)	p-value
BMI	$15.70 \pm 2.04$	$16.01 \pm 1.62$	0.1200 <sup>NS</sup>
WBC count (/mm <sup>3</sup> )	$7826 \pm 2453$	$7487 \pm 2363$	0.1846 <sup>NS</sup>
ESR (mm in 1 <sup>st</sup> hour)	$12.58 \pm 5.08$	$13.23 \pm 5.51$	0.2253 <sup>NS</sup>
CRP (mg/dl)	$2.64 \pm 1.03$	$2.52 \pm 1.43$	0.4290 <sup>NS</sup>
Serum calcium (mg/dl)	$9.37 \pm 0.91$	$9.52 \pm 0.93$	0.1129 <sup>NS</sup>
Serum phosphorus (mg/dl)	$3.58 \pm 1.18$	$3.70 \pm 1.17$	0.3443 <sup>NS</sup>
ALP (U/L)	$336.9 \pm 161$	$313.0 \pm 153$	0.1987 <sup>NS</sup>
Rheumatoid factor	Negative	Negative	-

BMI=body mass index, WBC=white blood cell, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, ALP=alkaline phosphatase.

All values were expressed as mean $\pm$ SD; NS=not significant as  $p > 0.05$ .

## DISCUSSION

We compared various laboratory parameters among children with growing pains and the healthy control group to determine whether these parameters were relevant for diagnosis. The results of tests were within normal range and were not found significant for diagnosis of growing pains. In our study, four-fifths of children with GP were between 5-10 years with a maximum one-third of children being between 5 to 6 years of age and the mean age was  $7.05 \pm 2.32$  years. Growing pains are commonly found in children aged between 3 and 12 years<sup>18</sup>. Boys were predominant, which correlates with the findings of Haque et al, Liao et al. and Li et al.<sup>5,13,14</sup>; however, girls' predominance were reported by several previous studies<sup>7,15,20</sup>. The sex ratio may vary between studies due to different adopted diagnostic criteria of GP and also the difference between the age ranges of the study population.

We performed several laboratory tests which are usually considered as parameters of inflammation and bone mineral status or indicators of bone homeostasis. The diagnostic relevance between these laboratory investigations and nonspecific musculoskeletal pain or GP is controversial; few studies have found a positive association with some parameters<sup>9,13,15</sup>, while others reported 'no association'<sup>7,21</sup>. Inflammatory markers are evaluated in patients as a part of the initial laboratory screening of the person suspected of having inflammation caused by an underlying disease or condition<sup>22</sup>. Leukocytosis or white blood cells (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are the most common and widespread laboratory tests used in the initial screening of inflammation and also in the diagnosis and monitoring of inflammatory conditions<sup>23</sup>. Although they lack disease specificity they can provide important information regarding inflammation<sup>24</sup>. Leukocytosis is considered the most consistent alteration of hematological count found in response to infection and inflammation. Plasma concentration of CRP rises during various inflammatory conditions and infection<sup>25</sup>. In our study, mean WBC counts and ESR were within normal limits in both GP and control groups. No significant leukocytosis or leukopenia and abnormally raised ESR were found among children with GP. We found that GP children had marginally higher mean levels of CRP than in the control group but results were mostly within the normal range in both groups.

Children with GP had a non-significant lower mean level of calcium and phosphorus but this was within the normal limit according to the age and sex of the children. Different types of relation of serum calcium and phosphorus with GP were reported by different authors. Asadi-Pooya et al. found serum calcium and phosphorus levels were nearly equal and normal in both groups<sup>7</sup>; Sharma et al. reported the level to be significantly higher in the GP group<sup>26</sup>, whereas Li et al. and Qamar et al. found it lower in GP children<sup>7,9</sup>. Serum calcium, phosphorus, and ALP are the bone turnover markers that are considered to be reflections of bone homeostasis. Serum ALP level is a valid marker of active bone formation that is found higher in growing children and during puberty<sup>27</sup>. We found that serum levels of ALP were nearly equal and within normal physiological ranges in both groups of children which were in contrast to Liao et al. and Qamar et al. who reported elevated ALP level in 37.5% and 38% of children with GP respectively<sup>7,9</sup>. This difference may be due to the dietary habits of the children especially calcium-containing foods, usages of minerals supplementations, geographical area, and also different study populations.

From the findings of the present study, it seems that GP is a clinical diagnosis and if Peterson's criteria of inclusion and exclusion are considered carefully, there will be a minimum requirement of laboratory tests to make a diagnosis. However, in case of atypical symptoms, the diagnosis should not be made before evaluating the other possible causes. Considering GP as a common paediatric complaint, it will also reduce the unnecessary costs of laboratory tests and also the discomfort to the child and families.

This study had certain limitations; it was a single-center study and the healthy control group was enrolled from hospital visiting children that may not represent the true community population of Bangladesh. It should also be noted that some other potentially important tests like serum vitamin D and ANA were not done in the present study which might have been beneficial for the evaluation of the disease.

## CONCLUSION

We would like to conclude that growing pains are diagnosed through a process of elimination, where a physician assesses a child's symptoms and overall health to rule out other potential causes of leg pain. There is no specific test for growing pains, and we should typically rely on a physical examination, medical history, and the child's description of their pain.

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