

# Camurati–Engelmann Disease: A Case-Based Review About an Ultrarare Bone Dysplasia

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## Abstract

Camurati–Engelmann disease or progressive diaphyseal dysplasia is a rare hereditary disease that results in a symmetrical hyperostosis of the long bones (cortical thickening) and/or the base of the skull. Camurati–Engelmann disease is also associated with myopathy and neurological manifestations. Clinically, Camurati–Engelmann disease typically presents with bone pain in the lower extremities, muscle weakness, and a wobbly, stilted gait. The disease is caused by mutations in the transforming growth factor-beta 1 gene. Up to date, about 300 cases have been described in the literature. In this case-based review, we present the clinical picture and genetic and radiological findings in a 20-year-old male patient we diagnosed with Camurati–Engelmann disease and our considerations in his treatment and compare the case to the literature. The diagnosis of Camurati–Engelmann disease was confirmed on patients' history, clinical and radiological findings, and genetic testing for transforming growth factor beta-1 mutation. The patient responded well to single therapy with zoledronic acid. Early diagnosis leads to improved clinical outcomes and increased quality of life in affected patients.

**Keywords:** Osteology, bone disease

## Introduction

Camurati–Engelmann disease (CED), also known as progressive diaphyseal dysplasia, is a rare autosomal dominant inherited pan-ethnic condition with more than 300 published cases with unknown prevalence.<sup>1–3</sup> The clinical picture is characterized by hyperostosis of the diaphysis of long bones of the extremities. In addition, involvement of the skull, pelvis, ribs, spine, bones of feet, and hands is described. The cortical thickening of the diaphysis involves both endosteal and periosteal bone surfaces. Endosteal bony sclerosis can result in a narrowed medullary canal and periosteal involvement with uneven cortical thickening and increased diameter.<sup>4,5</sup> The usual symptoms are limb pain, proximal muscle weakness, dull bone pain, waddling gait, and easy fatigue.<sup>1</sup> The onset of the disease ranges from birth to the age of 76 years.<sup>6</sup> Camurati–Engelmann disease is caused by domain-specific heterozygous mutations in the transforming growth factor-beta 1 gene (TGFB1) on chromosome 19q13,<sup>7,8</sup> which is still until today the only gene associated with CED.<sup>9</sup>

## Case Report

A 20-year-old male outpatient presented himself for the first time at our osteological university center in 2019. He had a medical history of diffuse and localized bone pain in both lower extremities for 4 years now with muscle weakness in his upper and lower limbs, poor muscle development of the legs in general, and recently developed a wide-based, slightly waddling gait accompanied by easy fatigue. So far, he had not experienced a loss of strength in the lower extremity. There was no fracture history.

Physical examination revealed an asthenic patient with prominent palpable tibial tuberosity on both sides, with normal passive and active movement of the knees and hips and a waddling gait. The patient had problems/pain on the right side while squatting. The spine was orthograde, stable, and normally mobile. The lower leg muscles were firm to the touch. The cranial nerve examination was also normal. There was slightly reduced muscle strength of both legs. There was no impairment of hearing or vision. Cognitive and motor development was normal.

The laboratory test showed the following elevated values: alkaline phosphatase 210 U/L (normal range, 35–129 U/L), tartrate-resistant acid phosphatase isoform 5b (TRAP5b) 4.8 U/l (reference range, males, 4.0 ± 1.4 U/L; Metra TRAP5b EIA Kit, Quindel Corporation, San Diego, Calif, USA), serum

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calcium (2.61 mmol/L; normal range: 2.40–2.55 mmol/L) and osteocalcin 53.2 ng/mL (reference range, 12–51.1 ng/mL), and the  $\beta$ -cross laps 0.914 ng/mL (reference range, males, 20–50 years < 0.573 ng/mL, Roche Diagnostics, Indianapolis, Ind, USA). Parathyroid hormone and 25-vitamin D3 were in the normal range.

Additionally, a bone biopsy from the right tibial tuberosity was performed 1 year earlier. The histological findings showed a clear accumulation of concentric layers in the form of "onion skin" in the periosteum, and the endosteal surface showed a compact layer of cancellous bone formation. An external skeletal scintigram showed multiple deposits in the lower leg without manifestations in the arms or skull.

Molecular testing of the TGF $\beta$ 1 sequence analysis revealed a missense mutation (c.652C>T; p.Arg218Cys), a known disease-causing mutation found in around 40% of CED patients.<sup>7</sup> The analysis was performed at the Institute for Medical Genetics and Human Genetics, BLINDED. A genetic analysis was later performed in the parents with negative results, so that a genetic spontaneous mutation can be assumed. Of note, there was no clinical or familial evidence of CED.

The bone mineral density (dual-energy absorptiometry) revealed osteopenia according to

WHO definition (T-score lumbar vertebrae 1–4: –1.8, total right femoral neck: –1.9).

Radiographs (Figure 1 and 2) showed unilateral irregular thickening (hyperostosis and endostosis) and massive cortical sclerosis of the diaphysis of the right tibia with suspicion of obstruction of the medullary canal. The left tibia was normal. Computer tomography (Figure 3) showed endosteal sclerosis causing obliteration of the medullary cavity of the right tibia, whereas the left tibia impressed with incipient endosteal sclerosis.

We diagnosed CED based on the medical history, typical clinical and imaging findings, and positive genetics with the identification of a heterozygous pathogenic variant in TGF $\beta$ 1 by molecular genetic testing.

Since a combination therapy with non-steroidal anti-rheumatic drugs (Ibuprofen 3  $\times$  800 mg) and prednisolone (15 mg/day) under gastric protection with pantoprazole 20 mg/day over a period of 1 year did not provide thorough relief of symptoms, an additional single dose of zoledronate (5 mg) was administered intravenously. This resulted in immediate pain relief. The steroid medication could be withdrawn within 6 months. After 6 months, the patient is now in pain remission with solely etoricoxib (60 mg daily) on demand. The previously, pathologically altered osteological markers (bone turnover) normalized within 3 months after the administration of the bisphosphonate zoledronic acid.



**Figure 2.** Lateral radiograph of the right tibia. The tibia revealed increased diaphyseal periosteal and endosteal density.

## Discussion

The case report describes the typical clinical features and symptoms, markers of bone metabolism, characteristic imaging findings, and clinical course with medical therapy. The diagnosis of CED was confirmed by genetic analysis of the TGF $\beta$ 1 gene.



**Figure 3.** Computed tomography of both tibiae. The bone CT showed endosteal sclerosis at the right tibia that causes obliteration of the medullary cavity and the left tibia impresses with initial endosteal sclerosis on the upper medial side. CT, computed tomography.

## Main Points

- Camurati–Engelmann disease (CED) is a rare hereditary disease that results in a symmetrical hyperostosis of the long bones (cortical thickening) and/or the base of the skull.
- Camurati–Engelmann disease should be suspected in individuals with proximal muscle weakness, limb pain, waddling gait, and typical radiological findings with symmetrical cortical thickening of the diaphysis.
- Molecular genetic testing (mutations of the transforming growth factor-beta 1 gene) is a confirmatory test and bone scintigraphy is a valuable diagnostic tool.
- Zoledronic acid may be an important therapeutic option in CED patients with persistent pain under standard pain medication (NSAIDs, glucocorticoids).
- Early diagnosis is important to improve the clinical outcome and quality of life of affected patients.



**Figure 1.** Anteroposterior radiographs of both tibiae and fibulae. The right tibia demonstrated increased density and diaphyseal sclerosis with suspicion of obstruction of the medullary cavity, the left tibiae was normal.

Considering the work of Yuldashev et al.<sup>10</sup> who described several groups based on clinical distinguishable presentation, our patient can be assigned to group II (patients presenting mainly with limb pain), whereas patients of group I mainly impress with motoric disorders at a young age. There was no history of CED in our patient. As a hereditary disease, familial accumulation of CED is described in the literature but is not mandatory for diagnosis. Nevertheless, family history must be obtained.

Typical radiological findings include hyperostosis of one or more long bones. Sclerosing bone dysplasia starts in the diaphysis of the long bones and can progress to the metaphysis and (in rare cases) epiphyses. Further findings include periosteal involvement with uneven cortical thickening and increased diameter. Endosteal bony sclerosis can lead to a narrowed medullary canal. Hyperostosis is usually symmetric in the appendicular skeleton, only in some cases asymmetric, and does not affect the spine.<sup>11</sup> Other radiologic findings that could be variably seen are skull involvement beginning at the base of the anterior and middle fossae often including the frontal bone,<sup>6,7,12</sup> mild osteosclerosis in the posterior neural arch of the spine and in parts of the flat bones corresponding to the diaphysis. However, sclerosing bone dysplasia is caused by a variety of disorders that have defects in the bone ossification pathway.<sup>11-13</sup>

In this light, an activating mutation of the TGF $\beta$ 1 gene was not only found in CED but also in Ribbing disease,<sup>14</sup> an osteosclerotic disease of the long bones, which is radiographically indistinguishable from CED and is usually associated with bone pain after puberty.<sup>15</sup> The phenotype of Ribbing disease was found in a 3-generation Japanese family with CED, whereupon it was suggested that CED and Ribbing disease represent the phenotypic variation of the same disorder.<sup>9,15,16</sup> However, unlike Ribbing's disease, CED presents with osteosclerosis of the skull base (56% of cases), the mandible (25% of cases), symmetry of bone involvement, and symptoms may begin in childhood.<sup>4,14,17,18</sup> Furthermore, CED shows progression into the metaphysis<sup>19</sup> and is associated with physical disability due to gait and neurological abnormalities.<sup>20</sup> Most importantly, CED seems to be progressing continuously, whereas Ribbing disease may become static.<sup>20</sup>

In this context, it is important to know other differential diagnoses disorders to CED. Only

few diseases have both the clinical and radiographic findings of CED;<sup>11,21</sup> however, differential diagnosis besides Ribbing's disease is given as follows: craniodiaphyseal dysplasia, Kenny–Caffey syndrome type 2, juvenile Paget disease, Ghosal hematodiaphyseal dysplasia, endosteal hyperostosis, and SOST-related sclerosing bone dysplasias including sclerostosis and van Buchem disease. In addition, mild hypophosphatasia can lead to hyperostosis and bone sclerosis and can lead to a waddling gait. The correct diagnosis is not made based on one examination or test alone but made in synopsis of physical examination, imaging, laboratory, biopsy, and/or genetics.

As briefly mentioned earlier, further clinical symptoms include headache and ophthalmopathy, which have been described in the second to third decade and audiovestibular and facial nerve involvements in the fourth to fifth decade.<sup>4,5</sup> Cranial nerve involvement occurs in 38%, with most deficits being hearing loss, visual problems, and facial paralysis. A conductive and/or sensorineural hearing loss is described in 19% of cases.<sup>4</sup> If orbital involvement occurs, blurred vision, proptosis, papilledema, epiphora, glaucoma, and subluxation of the globe are possible symptoms.<sup>4,22</sup> Extremely rare symptoms are dysphagia, incontinence, clonus, cerebellar ataxia, sensory loss, slurred speech, anemia, anorexia, hepatosplenomegaly, decreased subcutaneous tissue, atrophic skin, hyperhidrosis (hands and feet), delayed dentition, extensive caries, delayed puberty, and hypogonadism.<sup>4,10,23,24</sup>

Muskuloskeletal symptoms include reduced weakness and muscle mass of the proximal lower limbs, a wide-based/broad-legged, waddling gait in 48%–64%, joint contractures in 43%, and rarely a marfanoid body habitus.<sup>1,6</sup> Furthermore, musculoskeletal involvement can result in varying degrees of lumbar lordosis, kyphosis, scoliosis, coxa valga, radial head dislocation, genua valga, hallux valgus rigidus, flat feet, and frontal bossing.<sup>10</sup> Bone pain is reported in 68%–90% of cases of CED,<sup>1,6</sup> ranging from mild to severe. It is noteworthy that pain often increases with stress, activity, and cold conditions. An alteration of bone mineral density at the hip and femoral neck is described, while bone strength, as measured by bone impact micro indentation, was below normal in 3 siblings with CED.<sup>25</sup> An increased incidence of fractures has not been described, but when fractures occur, the healing process may be delayed.<sup>6</sup>

So far, no correlation between the genotype (variants of TGF $\beta$ 1 pathogenic mutations) and the phenotype (disease severity) has been found.<sup>26</sup>

Until now, no consensus medical guidelines have been developed. There is a paucity of evidence regarding the treatment of CED. So far, Non-steroidal anti-inflammatory drug(s) (NSAIDs), glucocorticoids (usually prednisone), bisphosphonates, and surgical treatment have been described.

At the time of presentation, the patient was treated for 1 year with a non-steroidal anti-rheumatic drug in combination with short-term prednisolone without adequate pain relief. Corticosteroids reduce bone density by decreasing the proliferation, differentiation, and bone formation of osteoblasts.<sup>27</sup> They also promote the proliferation and differentiation of osteoclast precursors.<sup>28</sup> In CED, corticosteroids act as antagonists of bone formation, and several reports have shown positive effects.<sup>1</sup> Since there was no adequate pain relief under this combination therapy, a single administration with the bisphosphonate zoledronic acid was performed (so far). The efficacy of bisphosphonates in reducing pain and clinical symptoms in CED has not been clearly defined, but there are some reports of bone pain relief under oral and intravenous pamidronate,<sup>29-31</sup> alendronate,<sup>32</sup> and zoledronic acid.<sup>33</sup> Therefore, the use of bisphosphonates is critically discussed in the treatment of CED. Before treatment with zoledronic acid, the biochemical markers of bone turnover were significantly elevated in our patient and returned to the normal range after treatment but also, and foremost, the treatment resulted in a reduction of the incapacitating pain. Besides its good effects on pain, zoledronic acid seems to inhibit bone remodeling and excessive bone formation due to the mutant TGF $\beta$ 1 in CED patients.<sup>33</sup> Therapeutic options are symptomatic and/or preventive, with the dominance of physiotherapy (mobilization, muscle building). Of note, biochemical markers of bone turnover could be considered as surrogate indices in active CED.<sup>33</sup> The following evidence of efficacy can also be found in the literature: calcitonin for pain relief,<sup>34</sup> Lorasatan reduced bone pain and increased physical activity,<sup>2,35</sup> and angiotensin II receptor blockers have also been described to be effective.<sup>1</sup> Clodronate infusion caused bone pain in one case and no improvement in other reports.<sup>36</sup>

Surgical interventions such as opening the medullary canal of the long bones and decompression of nerves and vessels are considered in cases of persistent pain but should only be performed if the disease has been histologically proven (pelvic crest biopsy).<sup>17</sup> Nevertheless, surgical procedures (reaming or fenestration to release intramedullary pressure due to compression) have a good effect on pain in Ribbing disease.<sup>20,37</sup>

## Conclusion

In summary, CED should be suspected in individuals with proximal muscle weakness, limb pain, waddling gait, and typical radiological findings with symmetrical cortical thickening of the diaphysis as we find in abnormal motor development in childhood. Molecular genetic testing (mutations of the TGF $\beta$ 1 gene) is a confirmatory test and bone scintigraphy is a valuable diagnostic tool. Given the existence of effective therapeutic modalities, early diagnosis is important to improve the clinical outcome and quality of life of affected patients. Zoledronic acid may be an important therapeutic option in CED patients with persistent pain under standard pain medication.

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**Peer-review:** Externally peer-reviewed.

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