

Elimination of Pain and Improvement of Exercise Capacity in Camurati-Engelmann Disease With Losartan

Ahila Ayyavoo, José G. B. Derraik, Wayne S. Cutfield, and Paul L. Hofman

Liggins Institute (A.A., J.G.B.D., W.S.C., P.L.H.), University of Auckland, Auckland 1142, New Zealand; and Department of Pediatric Endocrinology (W.S.C., P.L.H.), Greenlane Clinical Centre, Auckland District Health Board, Auckland 1051, New Zealand

Background: Camurati-Engelmann disease (CED) is a rare disorder, with approximately 250 described cases in the literature. Treatment options are limited and have been suboptimal so far.

Patient and Methods: A prepubertal girl aged 9 years was diagnosed with CED. Treatment with losartan was initiated at a daily dose of 0.75 mg/kg. Over a period of 12 weeks, the dose was gradually increased to 1.0 mg/kg/d. The patient was reviewed in clinic regularly and underwent thorough clinical assessments 9, 17, and 38 months after treatment initiation.

Results: The patient experienced marked clinical improvements with losartan. In particular, losartan treatment led to the complete elimination of the previously severe and incapacitating pain, with an increased ability to walk and perform physical activities. There was also a considerable improvement in body composition with increased lean and adipose tissue. Notably, the improvement in fat deposition had not been previously observed with other treatments in CED. Hematology, liver, and renal function tests were within normal ranges at presentation and remained so over the course of treatment.

Conclusions: In light of our findings, losartan may be a useful option in CED management. (*J Clin Endocrinol Metab* 99: 3978–3982, 2014)

Camurati-Engelmann disease (CED) is a rare disorder, with approximately 250 reported cases in the literature. The first case of a child with features of CED was described by Cockayne in 1920 (1). In 1922, Camurati (2) described “symmetrical hereditary osteitis” in a family with the manifestation of the disease over several generations. Subsequently, Engelmann (3) published a case of “osteopathica hyperostotica (sclerotisans) multiplex infantilis.” Typical clinical features are now classified as CED (OMIM 131300), which is described as “progressive diaphyseal dysplasia” to illustrate the progressive nature of changes in diaphyses (4).

A comprehensive review of 24 families with CED described in detail the clinical, radiological, and molecular data (5). CED is a rare autosomal dominant disorder,

characterized by cortical thickening of the diaphysis of the long bones, severe ostealgia in the extremities, peculiar waddling gait, easy fatigability, and proximal muscle weakness (5). Other clinical features include thin body habitus with reduced adiposity, hyperostosis of the skull, frontal bossing, and deafness (5, 6).

The pathophysiological bases of CED are mutations in latency-associated protein (LAP) increasing the amount of active TGF- β 1 (7, 8). TGF- β 1 is abundant in the bone matrix and is a cytokine involved in cell proliferation, migration, differentiation, apoptosis, angiogenesis, myogenesis, and various other biological processes (9). TGF- β 1 is a large precursor molecule consisting of active TGF- β 1 and a LAP (10). The LAP is noncovalently linked to active TGF- β 1, rendering it inactive because it masks

the receptor-binding domains of TGF- β 1 (10). Functionally, CED mutations have been classified into two groups. Exon 4 mutations destabilize the disulfide bridging of the LAPs, causing premature activation of the mature peptide. Exon 1 mutations rather affect secretion, leading to intracellular retention of the mutant protein. All mutations investigated so far increase TGF- β 1 activity (11). Active TGF- β 1 has a powerful inhibitory effect on osteoclast formation and bone resorption and a stimulatory effect on osteoblasts (12, 13), which are important regulatory steps in normal bone remodeling.

The hallmark of CED is hyperostosis of the long bone diaphyses, with modeling defects on the endosteal and periosteal surfaces (5). Metaphyseal involvement is seen occasionally (14). An increased tracer uptake by the bone is seen in scintigraphy (5), and mutation analysis can confirm the diagnosis. Although other clinical and biochemical features vary among patients, the most distressing symptom for these individuals is severe bone pain. TGF- β 1 also suppresses myoblast maturation, interferes with muscle repair (15), and suppresses adipogenesis (16). These factors may account for the poor muscle mass and reduced adiposity in patients with CED.

Patients have been treated with various pharmaceutical agents including glucocorticoids, bisphosphonates, calcitonin, and aspirin, as well as having undergone surgical procedures such as medullary reaming (5, 17). Unlike other therapies, angiotensin II type 1 receptor inhibition attenuates TGF- β 1 effects. Recent studies have revealed clinical improvement with losartan in Marfan syndrome (18), a condition analogous to CED with increased signaling by TGF- β 1 (19). Progressive aortic root enlargement (caused by excessive signaling of TGF- β 1) leads to aortic dissection in Marfan syndrome (18). This is mitigated by angiotensin receptor blockers that are antagonists of TGF- β 1 (18, 20). Angiotensin II receptor antagonists have also been shown to improve muscle pathology and congenital muscle dystrophies by reducing TGF- β 1 signaling (21). We report here the case of a child with CED who experienced marked clinical improvements with losartan.

Case Study

A 9-year-old girl presented to the Endocrinology Service at Starship Children's Hospital (Auckland, New Zealand). The patient had a history of poor weight gain since the age of 2 years, displayed a waddling gait, and had been experiencing pain of her limbs since the age of 4 years. Since 7 years of age, her situation had worsened considerably, so that her daily activities had been severely restricted. No-

tably, the patient's father reported experiencing similar but milder symptoms during his childhood. He has continued to tire easily in adulthood.

On examination, the girl was thin (Table 1). Her long bones were irregular to palpation, and she experienced exquisite tenderness over her limbs. X-rays showed cortical thickening of the diaphysis of long bones, with sclerosis of the base of the skull (Figure 1). Bone scintigraphy showed increased radioisotope uptake. All clinical features were consistent with a diagnosis of CED.

The patient underwent a thorough clinical assessment, including physical examination, blood pressure, and auxological measurements, as well as evaluation of pain scores on a Wong-Baker FACES analog scale (22). The child was subjected to a range of investigations that included a 6-minute walk test, whole-body dual-energy x-ray absorptiometry (DXA) scan, and assessment of bone health markers. Hematology, liver, and renal function were assessed, as well as mutation analysis.

Genetic analyses detected a mutation in exon 4, position C652T, causing an R218C amino acid substitution in the TGF- β 1 gene, located on chromosome 19q13. The same mutation was noticed in both father and daughter and confirmed the CED diagnosis at a molecular level.

Treatment with losartan was initiated at an oral daily dose of 0.75 mg/kg. This dose was chosen because it was within the recommended therapeutic dose range (0.6 to 1.4 mg/kg/d) observed to be beneficial for patients with Marfan syndrome (18). The patient had her blood pressure monitored on a daily basis in the home environment, whereas liver and renal function tests were periodically monitored (initially monthly, then 3-monthly after 6 months). Over a period of 12 weeks, the dose was gradually increased to 1.0 mg/kg/d. The patient was reviewed in clinic regularly and underwent thorough clinical assessments 9, 17, and 38 months after treatment initiation.

Pain

Pain was scored on an analog scale ranging from 0 (no pain) to 10 (worst possible pain) (22). Scores were evaluated in a number of areas, including proximal and distal sections of all long bones, trunk, and skull. At treatment initiation, the patient was in considerable distress, experiencing severe pain that was scored as 9. However, over the course of treatment there was a remarkable improvement in pain scores, so that by 38 months the child was completely pain-free (Table 1).

Six-minute walk test

With the major reduction in pain scores, the patient was able to increase her physical activity levels. As a result, after 9 months on losartan, the distance covered by the

Table 1. Results of Clinical Assessments of a 9-Year-Old Girl Diagnosed With Camurati-Engelmann Disease and Treated With Losartan for 38 Months

	At Presentation	9 mo	17 mo	38 mo
Age, y	9.3	10.1	10.7	12.5
Tanner stage				
Breast	1	1	1	2
Pubic hair	1	1	1	1
Cumulative pain score	9.00	1.75	0.25	0
6-min walk test, m	171	405	414	426
Blood pressure, mm Hg	90/60	96/60	104/66	90/60
Blood pressure SDS	−0.8/0.1	−0.3/0.1	0.3/0.6	−1.2/−0.1
Anthropometry				
Weight, kg	17.4	17.0	20.0	30.7
Weight SDS	−3.77	−4.25	−3.26	−1.90
Height, cm	123.6	128.3	131.7	139.6
Height SDS	−1.46	−1.39	−1.39	−1.79
Height SDS – MPH SDS	0.14	0.21	0.21	−0.19
Height velocity, cm/y		5.90	5.45	4.49
Body mass index SDS	−3.87	−5.06	−3.71	−1.36
DXA scans				
Whole-body less head BMC, g	465	517	578	807
Whole-body less head BMC SDS ^a	−1.96	−1.67	−1.32	−0.24
Whole-body less head BMD, g/cm ²	0.676	0.713	0.725	0.768
Whole-body less head BMD SDS ^a	1.40	1.31	0.99	0.58
Spinal BMD g/cm ²	0.575	0.568	0.603	0.635
Spinal BMD SDS ^a	0.69	0.16	0.21	−0.17
Total body fat, %	10.2	7.7	14.1	27.1
Fat mass, kg	1.70	1.26	2.69	7.86
Lean mass, kg	15.0	15.0	16.4	21.1

Pain scores are cumulative and were obtained from an analog scale ranging from 0 (no pain) to 10 (worst possible pain). Height SDS – MPH SDS represents height SDS adjusted for mid-parental height SDS. Blood pressure SDS values were calculated using data from Ref. 28.

^a Height-adjusted SDS.

child during the 6-minute walk test had increased from 171 to 405 m (a 237% improvement) (Table 1). This effect persisted at both 17 and 38 months (Table 1).

Blood pressure

At the time of first assessment, the patient's blood pressure was 90/60. Long-term treatment with losartan did not result in hypotension, and blood pressure SD score (SDS) remained within the normal range (Table 1). Although a more precise 24-hour ambulatory blood pressure monitoring was not performed, her blood pressure was still 90/60 after 38 months of treatment (Table 1).

Anthropometry

At treatment initiation, the patient's height was −1.46 SDS, but this was consistent with the mid-parental (target) height SDS of −1.60 (Table 1). There was a reduction in her height SDS over the course of treatment (Table 1), which was consistent with delayed pubertal growth. A bone age assessment performed at a chronological age of 12.5 years was assessed as 11 years, consistent with her pubertal stage.

In the first 9 months of treatment, the patient experienced some weight loss, so that weight SDS was reduced

from −3.82 to −4.57 SDS (Table 1). Data from DXA scans showed that this was a result of a reduction in fat mass from 10.2 to 7.7%, with lean mass being unchanged (Table 1). This may reflect increased levels of physical activity, in association with the reduction in pain scores and improvement in overall well-being due to treatment.

Importantly, by 38 months there was a marked improvement in weight and body composition (Table 1). Weight SDS had risen from −3.26 at 17 months to −1.90 at 38 months, with a similar improvement observed in body mass index SDS over the same period, which rose from −3.71 to −1.36 (Table 1). In addition to a steady rise in lean mass, the patient displayed a remarkable improvement in her ability to store adipose tissue, so that total body fat percentage rose markedly from 7.7 at treatment initiation to 27.1% at 38 months (Table 1).

Bone health

At presentation, there was evidence of abnormal bone turnover. Procollagen 1 NT peptide was 987 $\mu\text{g/L}$ (normal range, 280–830 $\mu\text{g/L}$), whereas bone-specific alkaline phosphatase was 78.5 $\mu\text{g/L}$ (normal range, 35–169 $\mu\text{g/L}$).

Although there were no radiological changes while on losartan, there were changes in bone mineral content

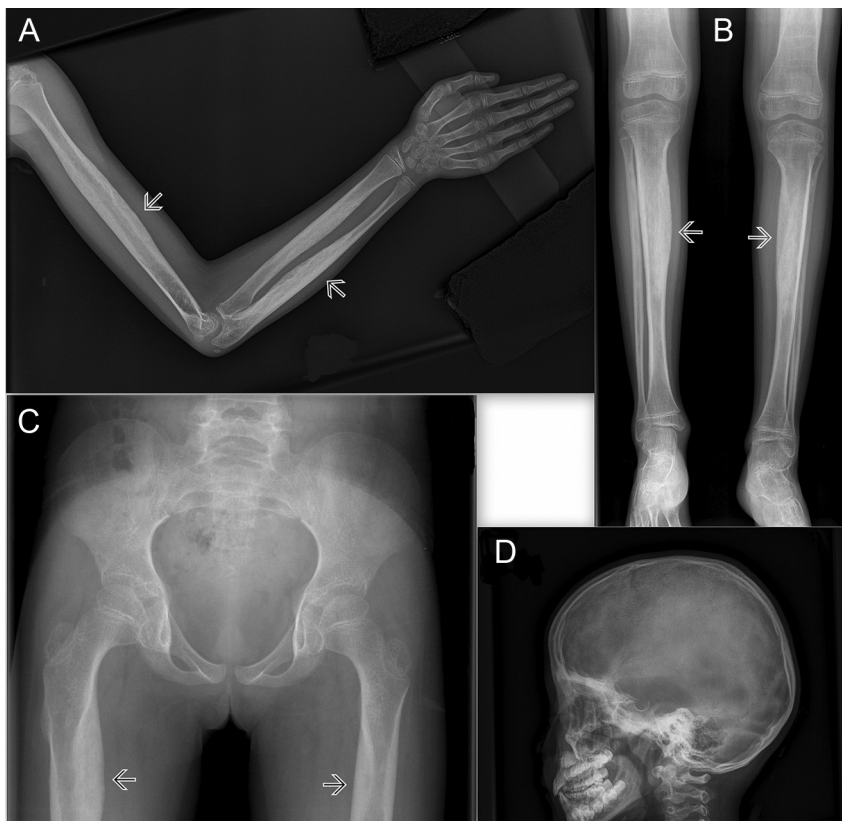


Figure 1. X-ray images showing features of Camurati-Engelmann disease in the patient at presentation. A, Thickening and irregularity of endosteal and periosteal sides of diaphyses of all long bones including radius, ulna, and metacarpals; B and C, tibiae, fibulae, and femora; and D, thickening of base of skull.

(BMC) and bone mineral density (BMD) on DXA scans (Table 1). In particular, there was a progressive increase in whole-body less head BMC toward the mean, changing from -1.96 SDS to -0.24 SDS over 38 months of treatment (Table 1). BMD progressively declined toward the mean, from 1.40 SDS to 0.58 SDS over the same period (Table 1).

Blood tests

Hematology, liver, and renal function tests were within normal ranges at presentation and remained so over the course of treatment (data not shown).

Discussion

We have shown that long-term treatment with losartan led to marked improvements in the symptoms of CED in a prepubertal child. In particular, losartan treatment led to the complete elimination of the previously severe and incapacitating pain, with an increased ability to walk and perform physical activities. There was also a considerable improvement in body composition with increased lean and adipose tissue. Despite an improvement in muscle mass and function, this was not completely normal, and

there was still evidence of weakness, with the subject continuing to have the characteristic waddling gait commonly described in CED. However, fat mass normalized over the 38 months of therapy, which was not due to estrogen-induced fat mass accumulation because she remained prepubertal over this time.

Losartan therapy also resulted in progressive normalization of BMC and BMD. These improvements occurred in the whole body as well as the spine, suggesting that the skeletal changes were not solely reflecting changes in high-density, non-weight-bearing bones such as the skull.

The apparent lack of growth with reducing height SDS over time likely reflects delayed puberty. The lack of puberty may be due to the patient's reduced fat mass, as it has been described in other lean CED subjects (23). Approximately 20% of CED patients are very lean, and this subgroup may be at risk of hypothalamic hypogonadism (5). As a result,

we will be following this girl to ensure that puberty progresses normally.

Glucocorticoids have been previously used for symptomatic pain relief (5) and for their effect on osteoclast and osteoblast functions that antagonize the pathological process in CED. However, glucocorticoid treatment has steroid-associated complications, including features of Cushing's syndrome, hypertension, reduction in BMD, and adverse effects in childhood growth. Bisphosphonates such as alendronate have also been reported to reduce pain in CED (17), but they increase bone density and could worsen this aspect of CED. Other therapies have also been tried (such as calcitonin and surgical cortical windowing) with variable results (24–27).

Losartan has an established safety profile in children and adults in various other disorders. In this patient with CED, losartan treatment was associated with marked improvements in the two major sources of distress—severe bone pain, and restricted physical activity. Notably, the improvement in fat deposition has not been previously observed with other treatments in CED. In light of these findings, losartan may be a useful option in the CED management. Long-term patient follow-up will clarify its efficacy and assess potential side effects.

Acknowledgments

We thank Dr Wim Van Hul and Karen Jennes for providing the genetic diagnosis and Dr Tim Cundy for valuable assistance and input.

Address all correspondence and requests for reprints to: Prof Paul Hofman, Liggins Institute, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand. E-mail: p.hofman@auckland.ac.nz.

Author contributions: A.A., P.L.H., and W.S.C. oversaw the treatment. A.A. and P.L.H. carried out clinical assessments. J.G.B.D. collected, compiled, and analyzed the data. J.G.B.D., A.A., and P.L.H. wrote the manuscript with input from W.S.C.

Disclosure Summary: The authors have no financial or non-financial conflicts of interest to disclose that may be relevant to this work.

References

- Cockayne EA. Case for diagnosis. *Proc Roy Soc Med*. 1920;13:132–136.
- Camurati M. Di uno raro caso di osteite simmetrica ereditaria degli arti inferiori. *Chir Organi Mov*. 1922;6:662–665.
- Engelmann G. Ein fall von osteopathia hyperostotica (sclerotisans) multiplex infantilis. *Fortschr Geb Roentgenstr Nukl*. 1929;39:1101–1106.
- Neuhauser EB, Shwachman H, Wittenborg M, Cohen J. Progressive diaphyseal dysplasia. *Radiology*. 1948;51:11–22.
- Janssens K, Vanhoenacker F, Bonduelle M, et al. Camurati-Engelmann disease: review of the clinical, radiological, and molecular data of 24 families and implications for diagnosis and treatment. *J Med Genet*. 2006;43:1–11.
- Sparkes RS, Graham CB. Camurati-Engelmann disease. Genetics and clinical manifestations with a review of the literature. *J Med Genet*. 1972;9:73–85.
- Kinoshita A, Saito T, Tomita H, et al. Domain-specific mutations in *TGFB1* result in Camurati-Engelmann disease. *Nat Genet*. 2000;26:19–20.
- Ghadami M, Makita Y, Yoshida K, et al. Genetic mapping of the Camurati-Engelmann disease locus to chromosome 19q13.1–q13.3. *Am J Hum Genet*. 2000;66:143–147.
- Janssens K, ten Dijke P, Ralston SH, Bergmann C, Van Hul W. Transforming growth factor- β 1 mutations in Camurati-Engelmann disease lead to increased signaling by altering either activation or secretion of the mutant protein. *J Biol Chem*. 2003;278:7718–7724.
- Tang Y, Wu X, Lei W, et al. TGF- β 1-induced migration of bone mesenchymal stem cells couples bone resorption with formation. *Nat Med*. 2009;15:757–765.
- Saito T, Kinoshita A, Yoshiura Ki, et al. Domain-specific mutations of a transforming growth factor (TGF)- β 1 latency-associated peptide cause Camurati-Engelmann disease because of the formation of a constitutively active form of TGF- β 1. *J Biol Chem*. 2001;276:11469–11472.
- Oreffo RO, Mundy GR, Seyedin SM, Bonewald LF. Activation of the bone-derived latent TGF β complex by isolated osteoclasts. *Biochem Biophys Res Commun*. 1989;158:817–823.
- Noda M, Camilliere JJ. In vivo stimulation of bone formation by transforming growth factor- β . *Endocrinology*. 1989;124:2991–2994.
- Brat HG, Hamoir X, Matthijs P, Lambin P, Van Campenhoutd M. Camurati-Engelmann disease: a late and sporadic case with metaphyseal involvement. *Eur Radiol*. 1999;9:159–162.
- Zimowska M, Duchesnay A, Dragun P, Oberbek A, Moraczewski J, Martelly I. Immunoneutralization of TGF β 1 improves skeletal muscle regeneration: effects on myoblast differentiation and glycosaminoglycan content. *Int J Cell Biol*. 2009;2009:659372.
- Zamani N, Brown CW. Emerging roles for the transforming growth factor- β superfamily in regulating adiposity and energy expenditure. *Endocr Rev*. 2011;32:387–403.
- Iba K, Takada J, Kamasaki H, et al. A significant improvement in lower limb pain after treatment with alendronate in two cases of Camurati-Engelmann disease. *J Bone Miner Metab*. 2008;26:107–109.
- Brooke BS, Habashi JP, Judge DP, Patel N, Loeyts B, Dietz HC III. Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. *N Engl J Med*. 2008;358:2787–2795.
- Habashi JP, Judge DP, Holm TM, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science*. 2006;312:117–121.
- Habashi JP, Doyle JJ, Holm TM, et al. Angiotensin II type 2 receptor signaling attenuates aortic aneurysm in mice through ERK antagonism. *Science*. 2011;332:361–365.
- Meinen S, Lin S, Ruegg MA. Angiotensin II type 1 receptor antagonists alleviate muscle pathology in the mouse model for laminin- α 2-deficient congenital muscular dystrophy (MDC1A). *Skelet Muscle*. 2012;2:18.
- Wong DL, Baker CM. Pain in children: comparison of assessment scales. *Pediatr Nurs*. 1988;14:9–17.
- Meczekalski B, Czyzyk A, Podfigurna-Stopa A, et al. Hypothalamic amenorrhea in a Camurati-Engelmann disease—a case report. *Gynecol Endocrinol*. 2013;29:511–514.
- Trombetti A, Cortes F, Kaelin A, Morris M, Rizzoli R. Intranasal calcitonin reducing bone pain in a patient with Camurati-Engelmann disease. *Scand J Rheumatol*. 2012;41:75–77.
- Inaoka T, Shuke N, Sato J, et al. Scintigraphic evaluation of pamidronate and corticosteroid therapy in a patient with progressive diaphyseal dysplasia (Camurati-Engelmann disease). *Clin Nucl Med*. 2001;26:680–682.
- Castro GR, Appenzeller S, Marques-Neto JF, Bértolo MB, Samara AM, Coimbra I. Camurati-Engelmann disease: failure of response to bisphosphonates: report of two cases. *Clin Rheumatol*. 2005;24:398–401.
- Bhadada SK, Sridhar S, Steenackers E, et al. Camurati-Engelmann disease (progressive diaphyseal dysplasia): reports of an Indian kindred. *Calcif Tissue Int*. 2014;94:240–247.
- National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(2 suppl 4th report):555–576.