DOI: 10.7860/JCDR/2026/85538.23839

Review Article

Orthopaedics Section

Camurati-Engelmann Disease: A Narrative Review of Clinical Features, Molecular Pathogenesis, Diagnosis, and Emerging Targeted Therapies

SHASHANK YADAV[1], RATNAKAR AMBADE[2], HARSH PATEL[3], ANSH KHANDUJA[4], BHAGYESH SAPKALE[5]

ABSTRACT

Camurati-Engelmann Disease (CED) is a very rare, autosomal-dominant type sclerosing bone dysplasia that is characterised by progressive diaphyseal hyperostosis, cortical thickening of long bones, along with variable involvement of skull-base. This narrative review synthesises the current evidence regarding clinical features, molecular basis, diagnosis, as well as management strategies of CED. Clinically, patients having CED, usually present in childhood or adolescence age with chronic pain in limbs, proximal muscle weakness, fatigability, along with a waddling gait, while cranial hyperostosis may lead to hearing impairment, cranial nerve deficits, or raised intracranial pressure. Pathogenic heterozygous mutations in Transforming Growth Factor Beta 1 (TGFB1), also less commonly Transforming Growth Factor Beta 1 (TGFB2), can cause disruption of the latency-associated peptide domain of TGF-β, which can result in excessive TGF-β activation along with downstream dysregulation of bone remodeling pathways. Diagnosis of CED primarily depends upon identification of typical clinical features, characteristic imaging findings of symmetric diaphyseal sclerosis, also definitive confirmation although is done using genetic testing. Management of CED is usually symptomatic, which is inclusive of analgesics, glucocorticoids, and emerging usage of angiotensin II receptor blockers such as losartan. Surgical decompression is usually reserved only for few cases which present with skull-base complications. Novel therapeutic strategies that target TGF-β axis, including receptor inhibitors, ligand traps, as well as Rho-GTPase pathway modulators, also represent promising options as disease-modifying treatment. Improved understanding of various molecular mechanisms for CED along with long-term clinical outcomes is essential for enhancing patient care and quality of life. This narrative review article focuses on uniquely merging updated molecular insights on dysregulated TGF-β signalling along with contemporary diagnostic algorithms, emerging targeted therapies, thus providing a consolidated, clinically oriented framework which is currently lacking in existing literature about CED.

Keywords: Bone remodeling, Cranial hyperostosis, Genetic testing, Hyperostotic disorders

INTRODUCTION

Camurati-Engelmann Disease (CED) also known as, Progressive diaphyseal dysplasia is a rare, usually autosomal-dominant sclerosing bone dysplasia characterised by symmetric cortical thickening and hyperostosis of the diaphyses of the long bones and variable involvement of the skull base [1]. Clinically it often presents in the childhood or early adulthood with progressive pain in bone (usually of the lower limbs), proximal muscle weakness along with waddling gait, easy fatigability, also in some patients, cranial-nerve symptoms or hearing impairment when the skull base is involved [1,2]. Radiography of the patient usually shows fusiform diaphyseal hyperostosis having endosteal and periosteal new bone formation that helps distinguish CED from other sclerosing bone disorders [3].

Pathogenic variants in the TGFB1 gene (which encode transforming growth factor-β1) are implicated in the majority of familial and many sporadic cases; these mutations alter signalling of TGF-β1 which are thought to drive the abnormal remodelling of bone that produces diaphyseal sclerosis [4]. The clinical course is of heterogeneous nature, few patients have severe, disabling pain as well as progressive skull involvement, while others can have mild or even subclinical disease; disease activity also often attenuates in adulthood [5,6]. Management is primarily directed at control of symptoms (analgesics, corticosteroids, bisphosphonates and surgical decompression can be performed for skull-base compromise cases), that is guided by clinical severity and radiologic progression of CED [3,5].

The condition was first identified in the early 20th century, when Cockayne provided an early description of it in year 1920, then Camurati suggested hereditary transmission shortly after that, and also Engelmann subsequently contributed additional clinical descriptions that together established the syndrome now having their names so termed as CED [7]. From the year 1990s to 2000s, several molecular studies identified TGFB1 mutations as the principal cause behind CED, thus transforming understanding of the disease from a purely descriptive clinicoradiological entity to one with a defined molecular mechanism and enabling genotype-phenotype correlations leading towards a targeted research into treatment aspect [2,7]. Globally, CED is an extremely rare condition, which is having nearby approximately 300 cases have been reported worldwide [1,8]. The estimated incidence is almost 1 in 1,000,000 individuals [8]. The actual prevalence of CED remains unknown because of its variable penetrance as well as phenotypic heterogeneity [1,8].

Clinical Features and Symptomatology of Camurati-Engelmann Disease

The CED, commonly presents in childhood or adolescence age having various musculoskeletal symptoms [9]. Bone pain, particularly present in the long bones, is very common and universal symptom, that is reported in all patients of CED [9]. This pain is often described as constant-aching, which worsens by performing any physical activity, stress, as well as cold weather [1,9]. CED affected individuals frequently have proximal muscle weakness, especially in the lower

limbs, reduced muscle mass, and easy fatigability [10]. These features thus contribute into a waddling, wide-based gait, while some patients also demonstrate joint contractures and low body mass index [10]. In addition to such musculoskeletal symptoms, cranial involvement is also reported commonly in CED [1,9]. Thickening of the skull base can lead to various neurological manifestations which are caused by nerve compression [4,9,11]. Patients in few cases develop hearing loss (sensorineural and/or conductive), headaches, visual disturbances, facial palsy or proptosis, and other cranial nerve deficits [4,12]. Increased intracranial pressure can be present, in few severe cases of CED [11,13].

In addition to its hallmark musculoskeletal symptoms, CED usually can also present with haematological, visceral abnormalities in few patients [14]. A classical case report by Crisp AJ and Brenton DP, described anaemia, leukopenia, increased erythrocyte sedimentation rate, as well as hepatosplenomegaly, that suggest CED may not be solely a bone disorder but may have systemic and inflammatory features [14]. In the large review of 100 patients from 24 families, there were few occasional occurrences of anaemia, leucopenia, and enlarged liver and spleen [15]. More recently, a cohort-study inclusive of 14 patients reported hepatosplenomegaly which was present in approximately half of the patients [16]. Endocrine dysfunction is not as such common but clinically important feature related to CED [13]. Skull-base hyperostosis in few severe cases might lead to hypopituitarism, as it is reported in a 20-year-old patient who developed secondary deficiencies of growth hormone, gonadotropins (hypogonadism), and cortisol, which is usually due to compression from overgrowth of bone and raised intracranial pressure [13]. Furthermore, such patients present mostly with delayed puberty as well as short stature [13].

Genetic Classification of Camurati-Engelmann Disease

The CED, is classically classified into two subtypes that is based on its genetic etiology. The first, common CED form is termed as Type I CED, which is associated with heterozygous mutations in the TGFB1 gene [15,17]. These mutations often cause disruption of Latency-associated Peptide (LAP) domain of TGF-β1, thus destabilising its latency complex and resulting in an increase in TGF-β1 signalling [18]. This increased TGF-β1 activation accelerates bone turnover, which results into the characteristic hyperostosis of the diaphyses of long bones and the skull base [15,18]. Type II CED is referred to genetically distinct sub-type in which no mutation of TGFB1 is present [19,20]. More recently, few pathogenic variants are also identified in TGFB2 in affected individuals, supporting the recognition of a genetically distinct Type II CED [20]. These TGFB2 mutations also localise to the LAP domain, further resulting into increased TGF-β2/Suppressor of Mothers Against Decapentaplegic (SMAD) signaling, although it can also produce subtly different clinical as well as radiographic features compared to classic TGFB1-mediated disease [20]. Classification of Camurati-Engelmann disease based on genetic aetiology is depicted in [Table/Fig-1] [15,17-20].

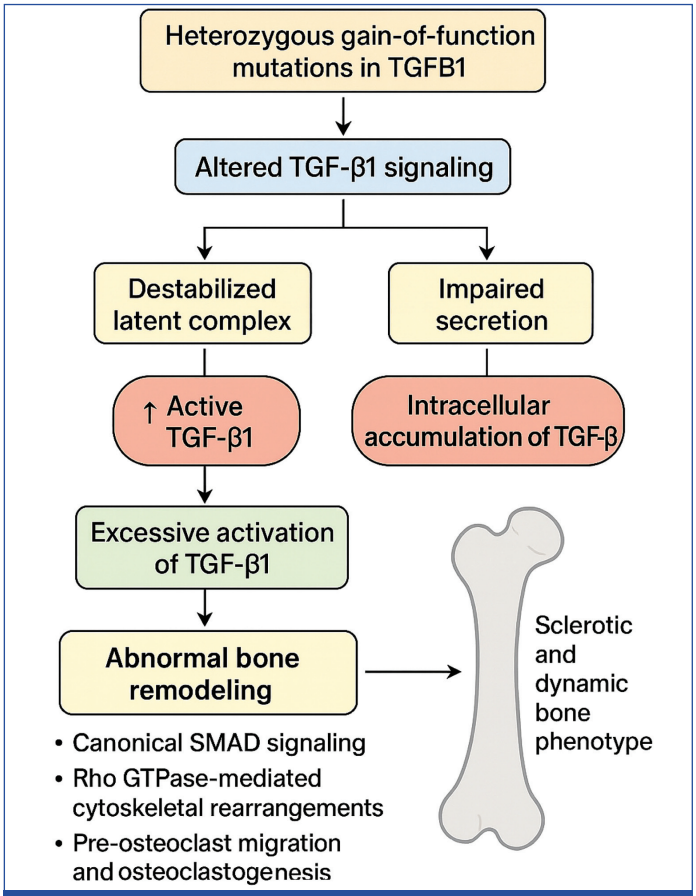
Features	Type I CED	Type II CED	References
Genetic basis	Heterozygous TGFB1 mutations	No TGFB1 mutation; TGFB2 variants identified	[15,17,19,20].
Affected protein domain	Mutations disrupt LAP domain of TGF-β1	TGFB2 mutations localise to LAP domain	[18,20].
Pathogenic mechanism	Destabilised TGF-β1 latency complex → Increased TGF-β1 signaling	↑ TGF-β2/SMAD signaling	[18,20].
Bone effects	Accelerated bone turnover → diaphyseal hyperostosis + skull base involvement	Similar changes with subtly different clinical/radiographic features	[15,18,20].
Prevalence	Classic and most common subtype	Genetically distinct, less common	[19,20].

[Table/Fig-1]: Classification of Camurati-Engelmann disease based on genetic aetiology.
TGFB1: Transforming growth factor beta 1, TGFB2: Transforming growth factor beta 2, TGF-β1: Transforming growth factor beta 1, TGF-β2: Transforming growth factor beta 2, LAP: Latency-associated peptide, SMAD: Suppressor of mothers against decapentaplegic

Molecular Pathogenesis and Dysregulated TGF-β1 Signaling in CED

The CED usually results from heterozygous gain-of-function mutations in the TGFB1 gene, which thereby encodes transforming growth factor-β1 (TGF-β1) in its latent form [21,22]. These genetic mutations cluster in the LAP region or signal peptide of the pro-TGF-β1 precursor [21]. Under normal conditions, TGF-β1 is secreted as a latent complex, where mature cytokine is bound to LAP (non covalently), thus preventing receptor binding until activation is triggered [21,22]. CED-related mutations thereby affect this latency in two main pathways [16,21]. First, mutations (such as R218C, H222D, C225R) destabilise the latent complex, so make it easier for TGF-β1 to become active; this leads to higher levels of active cytokine in the extracellular space [21]. Second, few other mutations (like L10_12dup, Y81H) cause impairment of secretion of latent form, thus causing intracellular accumulation; yet, even this retained mutant TGF-β1 can trigger enhanced transcriptional activity, suggesting there may be non canonical or intracellular signalling [16,21].

Excess activation of TGF-β1 resulting due to mutations drives abnormal bone remodelling: canonical SMAD signalling, Rho GTPase-mediated cytoskeletal rearrangements in pre-osteoclast migration and osteoclastogenesis [23]. The R218C mutation increases active Rho GTPases activity as well as cell-migration proteins (such as integrins), promoting preosteoclast migration along with bone resorption [23]. Moreover, osteoclastogenesis (and corresponding resorption) is markedly enhanced in cells which are derived from CED patients, consistent with elevated TGF-β1 signalling [21]. This imbalance between bone formation along with excessive resorption underscores the sclerotic as well as dynamic phenotype of bone in CED cases [21]. Molecular Pathogenesis of Camurati-Engelmann Disease is depicted in [Table/Fig-2].



[Table/Fig-2]: Molecular pathogenesis of Camurati-Engelmann disease [16,21-23].

Emerging evidence suggests about genotype-phenotype correlations in regard to CED. Mutations which are inclusive of cysteine residues within LAP domain (e.g., C225R) are usually associated having more severe disease due to marked destabilisation of latent complex, sustained TGF-β1 activation [21,22]. Mutations such as R218C have been linked usually to earlier onset as well as progressive diaphyseal hyperostosis [23]. The mutations such as H222D can show comparatively milder-variable expressivity [21]. However, considerable intrafamilial as well as interfamilial variability indicates towards additional genetic-environmental modifiers which likely influence clinical severity [21,23].

Diagnostic Approach to Camurati-Engelmann Disease

The CED is diagnosed through combination of characteristic clinical features with pathognomonic radiology [24]. Clinically, patients usually present having progressive pain in limb, proximal muscle weakness, easy fatigability as well as a waddling gait; cranial involvement may cause headache, cranial nerve symptoms or skull deformity in more severe cases [24]. Plain radiographs show symmetrical, fusiform diaphyseal cortical thickening along with endosteal sclerosis of the long bones also narrowing of the medullary canal [25,26]. Hyperostosis of skull-base is common which may present before symptoms appear prominently [11,25]. Cross-sectional imaging like Computed Tomography (CT) defines cortical hyperostosis as well as skull base changes, Magnetic Resonance Imaging (MRI) can point out marrow/soft-tissue involvement while whole-body MRI has been proposed for assessing extent of disease, also nuclear bone scans can show increased uptake in active diaphyseal lesions [27,28]. These imaging patterns are highly suggestive so often precede or outrank biochemical abnormalities [28].

Definitive confirmation of CED depends mainly on the genetic testing for identifying any possible pathogenic variants in TGFB1 [29]. Identification of a heterozygous TGFB1 mutation in an affected individual confirms the diagnosis and which further permits cascade testing as well as genetic counselling because most familial cases are autosomal dominant [29] . Routine laboratory tests are non specific (which may show normal or mildly altered bone turnover markers) also rarely bone biopsy is required [15,16]. In practice clinicians use the combination of appropriate history, examination, classic radiographic pattern, along with TGFB1 sequencing (usually that is targeted single-gene testing, multigene skeletal dysplasia panels, whole-exome sequencing when the phenotype is atypical) for making the final diagnosis of CED [25,30]. A high index suspicion along with early genetic confirmation of disease can help improve management, surveillance for skull-base complications, and family counselling in patients of CED [15]. Diagnosis of Camurati-Engelmann disease is summarised in [Table/Fig-3] [11,15,16,24-30].

Diagnostic domain	Key features/Findings	Notes/Utility	References
Clinical features	• Progressive limb pain • Proximal muscle weakness • Easy fatigability • Waddling gait • Cranial symptoms: headache, cranial nerve deficits, skull deformity	First-line diagnostic clues; often begin in childhood/ adolescence	[24].
Plain radiography	• Symmetrical fusiform diaphyseal cortical thickening • Endosteal sclerosis • Narrowed medullary canal • Skull-base hyperostosis	Classic/ pathognomonic imaging pattern	[25,26].
Skull-base changes	• Hyperostosis may appear early, sometimes before symptoms	Important for early detection	[11,25].
Computed Tomography (CT)	• Defines cortical hyperostosis • Superior for skull-base evaluation	Useful for severity assessment/ surgical planning	[27,28].
Magnetic Resonance Imaging (MRI)	• Shows marrow/soft-tissue involvement • Whole-body MRI for extent of disease	Helps evaluate early marrow changes	[27,28].
Bone Scintigraphy	• Increased radiotracer uptake in active diaphyseal lesions	Supports mapping of active disease	[27].
Genetic testing (definitive test)	• Identification of heterozygous TGFB1 pathogenic variant	Confirms diagnosis; allows cascade testing, counselling	[29]
Laboratory tests	• Non-specific • Normal or mildly altered bone turnover markers	Not diagnostic; supportive only	[15,16].
Bone biopsy	• Rarely required • Shows cortical thickening and sclerosis	Reserved for atypical/unclear cases	[15,16].
Genetic testing approaches	• Targeted TGFB1 sequencing • Multi-gene dysplasia panels • Whole-exome sequencing for atypical phenotypes	Used when phenotype unclear or broad testing required	[25,30].
Clinical approach tip	• High suspicion + early genetic confirmation improves management, surveillance, and counselling	Important when skull-base complications suspected	[15].

[Table/Fig-3]: Diagnosis of Camurati-Engelmann disease 11,15,16,24-30].

Comprehensive Management Approach for Camurati-Engelmann Disease

Medical treatment of CED is largely symptomatic as well as individualised [31]. Analgesics and anti-inflammatory agents are used for managing the pain, also systemic glucocorticoids (which include oral prednisone/deflazacort) frequently shown improvement in bone pain, fatigability and exercise tolerance in reported series, although long-term steroid side-effects limit their use [31,32]. In a paediatric case series, oral prednisone resulted into significant reduction in limb pain as well as improvement in ambulation; however recurrence of symptoms was observed following tapering thereby highlighting need for prolonged maintenance therapy in some patients [33].

Bisphosphonates are also under trial (which are pamidronate, alendronate, zoledronate) having mixed results, some case reports show benefit while others report no effect or even worsening activity, so they are not uniformly effective [34]. In a report describing two patients, one adult who underwent pamidronate infusion showed minimal clinical improvement despite of radiological stabilisation, whereas in another patient transient pain relief was noted without any adequately sustained functional benefit thus, underscoring about inconsistent therapeutic response [35].

Due to pathogenic TGFB1 gain-of-function as causation in most cases of CED, angiotensin II receptor blockers (such as losartan) are emerging as a rational, steroid-sparing adjunct which is shown in several case reports/series and small case-based reviews, with marked symptom improvement described in some patients; however, this evidence remains limited to case studies and small cohorts [32,36]. In a case of an adolescent patient having an R218C mutation, losartan therapy was associated with marked reduction in bone pain as well as improved exercise tolerance over one year of follow-up [32]. In another adult case refractory to corticosteroids; addition of losartan further enabled successful steroid tapering along with sustained symptomatic improvement [36].

Supportive measures like physiotherapy, gait training, analgesic optimisation, regular monitoring of functional status of patient and bone pain, along with treating various complications such as anaemia, growth/ delayed puberty in children when present are important components of conservative care [1,5,37]. Surgical management of CED is reserved only for cases which have anatomical complications such as skull-base hyperostosis and focal diaphyseal defects [38]. In a reported neurosurgical case, cranial vault decompression was performed for raised intracranial pressure due to severe cranial hyperostosis which further resulted into improvement of headaches and papilloedema [39].

Decompressive neurosurgical and otolaryngologic procedures for cases having cranial-nerve entrapment, optic nerve, foramen-magnum and brainstem compression, symptomatic intracranial hypertension, along with severe craniofacial deformity may provide neurological improvement in selected patients but are technically challenging because of sclerotic bone and altered landmarks outcomes [38,40]. In a case, internal auditory canal decompression further led to stabilisation of facial nerve paresis as well as vestibulocochlear symptoms while medullary canal drilling in a separate adult patient having refractory diaphyseal pain provided significant symptomatic relief [40]. So, the management approach for CED must be personalised, while balancing symptomatic benefit over side effects, as well as surgical intervention to be reserved only for clearly defined anatomical indications [40].

Emerging Therapeutic Strategies for Camurati-Engelmann Disease

Emerging strategies for CED focus on methods which can directly normalise hyperactive TGF-β axis along with its downstream effects rather than only treating symptoms [23,41,42]. Among these approaches, TGF-β neutralising antibodies and ligand traps are considered closest to potential clinical translation as similar biologic agents which target the TGF-β pathway are already undergoing early-phase of their clinical trials in other TGF-β–mediated disorders thereby it helps in potentially shortening repurposing timelines for CED [41,42]. Preclinical work results have shown that bone-targeted delivery of TGF-β type I receptor inhibitors can cause reduction of aberrant TGF-β signalling in bone while improving bone-remodelling abnormalities, thus provides a proof-of-principle suggesting that receptor-level blockade with skeletal selectivity is possible in CED cases [42]. However, before direct human application; issues which are related to systemic toxicity, off-target effects, dose optimisation as well as long-term skeletal safety must be addressed through carefully designed phase I/II studies [41,42].

Pan-TGF-β neutralising antibodies and ligand-traps or decoy receptors which have also demonstrated efficacy in animal models of TGF-β-driven musculoskeletal pathology including reduction of TGF-β-mediated muscle weakness, thus further supporting antibody/ biologic strategies as a translational route for treatment of CED [41]. Regulatory pathways for ultra-rare diseases such as CED can benefit from orphan drug designation which can help to provide incentives including market exclusivity, fee reductions as well as accelerated review [41]. However, small number of patients along with lack of validated surrogate endpoints remain very significant barriers to trial design and approval [41].

More recently, few studies which implicate Rho GTPase-mediated cytoskeletal remodelling downstream of excessive TGF-β activity identify druggable intracellular effectors, such as inhibitors of Rho signalling or related kinases as alternative targets for rebalancing bone turnover [23]. These intracellular targets still remain at an earlier stage of drug development as well as substantial preclinical validation, biomarker identification, also multicentric patient registry collaboration will be essential before translation into clinical trials becomes feasible [23].

Importantly, even if biologic or targeted therapies reach upto the level of clinical approval, patient access, cost considerations can significantly influence real-world implementation usually in low and middle-income settings where access to high-cost biologics is still very limited [23,41]. Early interactions with health-technology assessment bodies as well as exploration of repurposed-biosimilar agents can prove helpful to mitigate these challenges [23,41,42]. Management and Emerging Therapeutic Strategies in Camurati-Engelmann Disease are mentioned in [Table/Fig-4] [1,5,23,31,32,34,36,37,38,40,41,42].

Physical Quality-of-Life Limitations in Camurati-Engelmann Disease

Patients with CED experience a substantial reduction in Health-related Quality of Life (HRQoL) that is driven usually by the presence of severe physical symptoms rather than by impaired mental health: a recent SF-12-based case series found a markedly reduced Physical Component Summary score (PCS-12 median ≈29.8 vs population mean 50.0) while the Mental Component Summary (MCS) score was close to population norms [43]. This decrease in physical HRQoL mirrors the high prevalence of fatigue, limb and muscle pain, impaired gait and reduced exercise tolerance that characterise CED which commonly limit ambulation and daily activities in patients [1,43]. Importantly, several published case reports and series show that symptom-directed therapies for example glucocorticoids and

Category	Intervention/ Strategy	Description (based on provided content only)	References
Medical management	Analgesics and Anti-inflammatory agents	Used for symptomatic control of bone pain and musculoskeletal discomfort.	[31].
	Systemic glucocorticoids (prednisone, deflazacort)	Improve bone pain, fatigability, and exercise tolerance; long-term use limited by steroid-related adverse effects.	[31,32].
	Bisphosphonates (pamidronate, alendronate, zoledronate)	Have shown mixed results in case reports; may improve, show no effect, or worsen symptoms; not uniformly effective.	[34].
	Angiotensin II receptor blockers (e.g., losartan)	Rationale based on TGFB1 gain-of-function; emerging steroid-sparing option. Several case reports show notable symptomatic improvement, but evidence limited to small studies.	[32,36].
	Supportive care	Includes physiotherapy, gait training, analgesic optimisation, functional monitoring, and management of complications (anemia, delayed puberty, growth issues).	[1,5,37].
Surgical management	Indications	Reserved for structural complications: skull-base hyperostosis, focal diaphyseal defects.	[38].
	Neurosurgical / ENT decompression	Used for cranial-nerve entrapment, optic nerve compression, foramen magnum stenosis, brainstem compression, intracranial hypertension, severe craniofacial deformities. Technically challenging due to dense sclerotic bone.	[38,40].
	Surgical approach	Only for clearly defined anatomic indications; individualised to risk-benefit profile.	[40].
Emerging therapeutic strategies	TGF-β type I receptor inhibitors (bone-targeted)	Preclinical studies show reduction in aberrant TGF-β signaling and improvement in bone-remodeling abnormalities; demonstrates feasibility of skeletal-selective receptor blockade.	[42].
	Pan-TGF-β neutralising antibodies / ligand traps	Shown efficacy in animal models of TGF-β-driven musculoskeletal disease; reduce TGF-β-mediated muscle weakness; support potential use of biologics for CED.	[41].
	TGF-β decoy receptors	Serve as ligand traps to neutralise excessive TGF-β activity; effective in preclinical models.	[41].
	Rho GTPase / Rho-kinase pathway inhibitors	Target downstream cytoskeletal remodeling driven by aberrant TGF-β signaling; offer an alternative intracellular therapeutic target for restoring bone turnover balance.	[23].

[Table/Fig-4]: Management and emerging therapeutic strategies in Camurati-Engelmann Disease [1,5,23,31,32,34,36,37,38,40,41,42].

angiotensin-II receptor antagonists such as losartan, can substantially reduce pain and improve walking capacity and exercise tolerance in some patients [31,44]. However available evidence is largely limited to individual case observations without any specific controlled trials therefore magnitude and consistency of benefit remain uncertain [31,44]. These reported improvements although very encouraging but should be interpreted cautiously until they are validated in larger systematic studies [31,44].

In a case series which was evaluating HRQoL in patients having CED using the SF-12 instrument, markedly reduced PCS scores were observed, whereas MCS scores were close to population norms thereby indicating about physical impairment being predominant driver of reduced HRQoL [43]. In another reported case of an 18-year-old patient who was treated using combined glucocorticoid and losartan therapy, significant reduction into limb pain as well as improvement in exercise tolerance were documented thus, accompanied by enhanced daily functional capacity [32]. Similarly, a 27-year-old female having refractory disease further experienced substantial pain relief along with improved mobility after initiation of losartan as a steroid-sparing agent [45]. In a paediatric case which was managed using losartan monotherapy, elimination of severe bone pain and measurable improvement in walking ability were noted thereby indirectly reflecting improvement in physical QoL domains [46]. Collectively, all these reports demonstrate that targeted symptomatic therapy can further translate into meaningful functional and HRQoL gains in patients suffering with CED.

Limitation(s)

The present narrative review has certain limitations, including dependence on case reports and small case series, absence of systematic review methodology, and limited long-term therapeutic outcome data due to the rarity of the disease.

CONCLUSION(S)

Camurati-Engelmann disease is really a very rare, genetically mediated skeletal dysplasia where dysregulated signalling of TGF-β drives progressive diaphyseal hyperostosis, diverse musculoskeletal as well as cranial manifestations. Early diagnosis through characteristic clinical features, radiographic patterns, also confirmatory TGFB1/TGFB2 testing is essential for adequate management along with family counselling. Treatment of CED remains mainly symptomatic, which is done with glucocorticoids, losartan, supportive therapies, and selective surgical interventions offering variable benefit. Molecularly targeted approaches aim towards modulation of the TGF-β pathway which hold promise as emerging disease-modifying therapy for CED. Continued clinical research using long-term cohort data are important for improving outcomes in affected patients.

REFERENCES

[1] Wallace SE, Wilcox WR. Camurati-Engelmann Disease. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993. [cited 2025 Nov 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1156/. PMID: 20301335.

[2] Kinoshita A. [Camurati-Engelmann disease]. Nihon Rinsho Jpn J Clin Med. 2015;73(12):2149-59. PMID: 26666167.

[3] Li MML, Chung KY, Ng AWH, Chiu KH. Progressive diaphyseal dysplasia: A rare bone disorder with alarming radiographs. Hong Kong Med J. 2020;26(6):538.e1-538.e3. Doi: 10.12809/hkmj208498. PMID: 33350969.

[4] Van Hul W, Boudin E, Vanhoenacker FM, Mortier G. Camurati-Engelmann Disease. Calcif Tissue Int. 2019;104(5):554-60. Doi: 10.1007/s00223-019-00532-1. PMID: 30721323.

[5] de Bonilla Damiá Á, García Gómez FJ. Camurati-Engelmann disease. Reumatol Clin. 2017;13(1):48-49. English, Spanish. Doi: 10.1016/j.reuma.2015.12.004. Epub 2016 Jan 29. PMID: 26830437.

[6] Dubost JJ, Soubrier M. Camurati-Engelmann disease or Ribbing disease. Joint Bone Spine. 2021;88(3):105130. Doi: 10.1016/j.jbspin.2021.105130. PMID: 33484859.

[7] Hughes P, Hassan I, Que L, Mead P, Lee JH, Love DR, et al. Observations on the Natural History of Camurati-Engelmann Disease. J Bone Miner Res Off J Am Soc Bone Miner Res. 2019;34(5):875-82. Doi: 10.1002/jbmr.3670. PMID: 30690794.

[8] Wallace SE, Wilcox WR. Camurati-Engelmann Disease. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993. [cited 2025 Nov 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1156/. PMID: 20301335.

[9] Klemm P, Aykara I, Lange U. Camurati-Engelmann Disease: A Case-Based Review About an Ultrarare Bone Dysplasia. Eur J Rheumatol. 2023;10(1):34-38. Doi: 10.5152/eurjrheum.2023.21115. PMID: 36880809. PMCID: PMC10152113.

[10] Wahba Y, Abdel Ghaffar NA, Shaltout A, Elsharkawy A. Camurati-Engelmann disease: New clinical insights in an Egyptian case report. J Orthop Sci Off J Jpn Orthop Assoc. 2020 May;25(3):529-32. Doi: 10.1016/j.jos.2017.09.004. PMID: 28943142.

[11] Carlson ML, Beatty CW, Neff BA, Link MJ, Driscoll CLW. Skull base manifestations of Camurati-Engelmann disease. Arch Otolaryngol Head Neck Surg. 2010 Jun;136(6):566-75. Doi: 10.1001/archoto.2010.68. PMID: 20566907.

[12] Mundra V, Taxel P. Camurati-Engelmann disease a rare cause of bone pain. Conn Med. 2012 Jan;76(1):33-37.. PMID: 22372177.

[13] Das L, Dhiman V, Dutta P, Sood A, Prakash M, Kaur S, et al. Camurati-Engelmann Disease Complicated by Hypopituitarism: Management Challenges and Literature Review of Outcomes With Bisphosphonates. AACE Clin Case Rep. 2022;8(2):58-64. Doi: 10.1016/j.aace.2021.10.002. PMID: 35415221. PMCID: PMC8984528.

[14] Crisp AJ, Brenton DP. Engelmann's disease of bone--a systemic disorder? Ann Rheum Dis. 1982 Apr;41(2):183-88. Doi: 10.1136/ard.41.2.183. PMID: 7073346. PMCID: PMC1000905.

[15] Janssens K, Vanhoenacker F, Bonduelle M, Verbruggen L, Van Maldergem L, Ralston S, 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):01-11. Doi: 10.1136/jmg.2005.033522. PMID: 15894597. PMCID: PMC2564495.

[16] Liang H, Jiajue R, Qi W, Liu W, Chi Y, Jiang Y, et al. Clinical characteristics and the influence of rs1800470 in patients with Camurati-Engelmann disease. Front Endocrinol. 2022;13:1041061. Doi: 10.3389/fendo.2022.1041061. PMID: 36339419. PMCID: PMC9631481.

[17] Yuldashev AJ, Shin CH, Kim YS, Jang WY, Park MS, Chae JH, et al. Orthopedic Manifestations of Type I Camurati-Engelmann Disease. Clin Orthop Surg. 2017;9(1):109-15. Doi: 10.4055/cios.2017.9.1.109. PMID: 28261436. PMCID: PMC5334020.

[18] Campos T, Uchoa E, Santos V, Zatarin R, Benício R, Gomes C, et al. Phenotypic Variability in Camurati-Engelmann Disease: A Case Report of a Family with the c.653G>A Pathogenic Variant in the TGFB1 Gene. Genes. 2024;15(11):1354. Doi: 10.3390/genes15111354. PMID: 39596554. PMCID: PMC11593567.

[19] Mumm S, Paz-Ibarra JL, Campeau PM, Garrido-Carrasco E, Baker JC, Pino-Nina E, et al. Transforming growth factor, beta-2 gene mutation causes autosomal dominant Camurati-Engelmann disease, type 2 (OMIM % 606631). Bone. 2025;197:117477. Doi: 10.1016/j.bone.2025.117477. PMID: 40204055.

[20] Wang Z, Kometani M, Zeitlin L, Wilnai Y, Kinoshita A, Yoshiura KI, et al. Heterozygous mutations in the straitjacket region of the latency-associated peptide domain of TGFB2 cause Camurati-Engelmann disease type II. J Hum Genet. 2024;69(11):599-605. Doi: 10.1038/s10038-024-01274-1. PMID: 39014191.

[21] McGowan NWA, MacPherson H, Janssens K, Van Hul W, Frith JC, Fraser WD, et al. A Mutation Affecting the Latency-Associated Peptide of TGFβ1 in Camurati-Engelmann Disease Enhances Osteoclast Formation in Vitro. J Clin Endocrinol Metab. 2003;88(7):3321-26. Doi: 10.1210/jc.2002-020564.

[22] Janssens K, ten Dijke P, Ralston SH, Bergmann C, Van Hul W. Transforming growth factor-beta 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(9):7718-24. Doi: 10.1074/jbc.M208857200. PMID: 12493741.

[23] Chen Q, Yao Y, Chen K, Chen X, Li B, Li R, et al. Aberrant activation of TGF-β1 induces high bone turnover via Rho GTPases-mediated cytoskeletal remodeling in Camurati-Engelmann disease. Front Endocrinol. 2022;13:913979. Doi: 10.3389/fendo.2022.913979. PMID: 36325441. PMCID: PMC9621586.

[24] Alkaya A, Yıldız AE, Bağlan E, Özdel S. Unveiling the uncommon: Diagnostic journey of camurati-engelmann disease in a paediatric patient. Pediatr Rheumatol Online J. 2024;22(1):89. Doi: 10.1186/s12969-024-01016-9. PMID: 39379987. PMCID: PMC11460205.

[25] Uezato S, Dias G, Inada J, Valente M, Fernandes E. Imaging aspects of Camurati-Engelmann disease. Rev Assoc Medica Bras 1992. 2016;62(9):825-27. Doi: 10.1590/1806-9282.62.09.825. PMID: 28001254.

[26] Bartuseviciene A, Samuilis A, Skucas J. Camurati-Engelmann disease: Imaging, clinical features and differential diagnosis. Skeletal Radiol. 2009;38(11):1037-43. Doi: 10.1007/s00256-008-0642-1. PMID: 19214502.

[27] Xie P, Huang JM, Li HL, Huang XJ, Wei LG. Camurati-Engelmann disease-a rare cause of tetany identified on bone scintigraphy: A case report. Medicine (Baltimore). 2017;96(27):e7141. Doi: 10.1097/MD.0000000000007141. PMID: 28682867. PMCID: PMC5502140.

[28] Corrêa DG, Canella C, de Queiroz Campos Araújo AP, Mendonça S, Costa FM. Whole-Body Magnetic Resonance Imaging in Camurati-Engelmann Disease. JBMR Plus. 2020;4(4):e10357. Doi: 10.1002/jbm4.10357. PMID: 32258971. PMCID: PMC7117840.

[29] Tao XH, Yang XG, Wang ZY, Xu Y, Lin XY, Xu T, et al. Clinical characteristics and identification of a novel TGFB1 variant in three unrelated Chinese families with Camurati-Engelmann disease. Mol Genet Genomic Med. 2022;10(5):e1922. Doi: 10.1002/mgg3.1922. PMID: 35315241. PMCID: PMC9034665.

[30] Nagra D, Russell MD, Alveyn E, Birring SS, Elias D, Balachandran S, et al. Diagnosing Camurati-Engelmann disease-the age of whole-exome sequencing. Rheumatol Oxf Engl. 2023;62(7):e221-22. Doi: 10.1093/rheumatology/keac670. PMID: 36519831. PMCID: PMC10321082.
[31] Kim YM, Kang E, Choi JH, Kim GH, Yoo HW, Lee BH. Clinical characteristics and treatment outcomes in Camurati-Engelmann disease: A case series. Medicine (Baltimore). 2018;97(14):e0309. Doi: 10.1097/MD.0000000000010309. PMID: 29620655. PMCID: PMC5902284.
[32] Cui L, Li Q, Guan W, Yu W, Li X, Xia W, et al. Improvement of Bone Health and Initiation of Puberty Development in Camurati-Engelmann Disease With Glucocorticoid and Losartan Treatment: A Case Report and Review of Literature. Front Endocrinol. 2022;13:882144. Doi: 10.3389/fendo.2022.882144. PMID: 35784539. PMCID: PMC9247158.
[33] Slemp WH, Hunter JD, Walsh ET, Constantacos C, Crudo DF. Insights Into Management of Camurati-Engelmann Disease: A Case Series of Three Siblings. Int J Clin Pediatr. 2020;9(4):130-34.
[34] Baroncelli GI, Ferretti E, Pini CM, Toschi B, Consolini R, Bertelloni S. Significant Improvement of Clinical Symptoms, Bone Lesions, and Bone Turnover after Long-Term Zoledronic Acid Treatment in Patients with a Severe Form of Camurati-Engelmann Disease. Mol Syndromol. 2017;8(6):294-302. Doi: 10.1159/000479859. PMID: 29230158. PMCID: PMC5701277.
[35] Castro GRW, 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(4):398-401. Doi: 10.1007/s10067-004-1056-7. PMID: 15660289.
[36] Abdulla MC. Camurati-Engelmann Disease with Good Treatment Response to Losartan. Indian J Nucl Med IJNM Off J Soc Nucl Med India. 2019;34(3):223-25. Doi: 10.4103/ijnm.IJNM_44_19. PMID: 31293304. PMCID: PMC6593949.
[37] Mwasamwaja AO, Mkwizu EW, Shao ER, Kalambo CF, Lyaruu I, Hamel BC. Camurati-Engelmann disease: A case report from sub-Saharan Africa. Oxf Med Case Rep. 2018;2018(7):omy036. Doi: 10.1093/omcr/omy036. PMID: 30034812. PMCID: PMC6049015.
[38] Saboya F, Medina A, Cadavid S, Fuentes R, Jiménez-Canizales CE. Surgery Treatment of an Adult Patient with Camurati-Engelmann Disease: A Case Report. JBJS Case Connect. 2021;11(3). Doi: 10.2106/JBJS.CC.20.01042. PMID: 34351871.
[39] Mocco J, Komotar RJ, Zacharia BE, Feldstein NA, Bruce JN. Aggressive cranial vault decompression for cranial hyperostosis: Technical case report of two cases. Neurosurgery. 2005;57(1 Suppl):E212; discussion E212. Doi: 10.1227/01.neu.0000163686.75095.b8. PMID: 15987595.
[40] Achahbar SE, Somers T, Van Havenbergh T. Decompression of the internal auditory canal via the retrosigmoid approach in a patient with Camurati-Engelmann disease: Illustrative case. J Neurosurg Case Lessons. 2021;1(4):CASE2039. Doi: 10.3171/CASE2039. PMID: 36131584. PMCID: PMC9628102.
[41] Waning DL, Mohammad KS, Reiken S, Xie W, Andersson DC, John S, et al. Excess TGF-β mediates muscle weakness associated with bone metastases in mice. Nat Med. 2015;21(11):1262-71. Doi: 10.1038/nm.3961. PMID: 26457758. PMCID: PMC4636436.
[42] Qin Y, Tang S, Zhen G, Ding Q, Ding S, Cao X. Bone-targeted delivery of TGF-β type 1 receptor inhibitor rescues uncoupled bone remodeling in Camurati-Engelmann disease. Ann N Y Acad Sci. 2018;1433(1):29-40. Doi: 10.1111/nyas.13941. PMID: 30091466.
[43] Peláez P, Peris P, Guañabens N. Health-related quality of life in patients with Camurati-Engelmann disease: A case series study. Med Clin (Barc). 2025;165(4):107043. Doi: 10.1016/j.medcli.2025.107043. PMID: 40513308.
[44] Ayyavoo A, Derraik JGB, Cutfield WS, Hofman PL. Elimination of pain and improvement of exercise capacity in Camurati-Engelmann disease with losartan. J Clin Endocrinol Metab. 2014;99(11):3978-82. Doi: 10.1210/jc.2014-2025. PMID: 25140400.
[45] Agarwal K, Rajan R, Paul J, Cherian KE, Kapoor N, Paul TV. Losartan as a Steroid-Sparing Adjunct in a Patient With Features of Refractory Camurati-Engelmann Disease. AACE Clin Case Rep. 2022;8(2):54-57. Doi: 10.1016/j.aace.2021.08.002. PMID: 35415233. PMCID: PMC8984203.
[46] Simsek-Kiper PO, Dikoglu E, Campos-Xavier B, Utine GE, Bonafe L, Unger S, et al. Positive effects of an angiotensin II type 1 receptor antagonist in Camurati-Engelmann disease: A single case observation. Am J Med Genet A. 2014;164A(10):2667-71. Doi: 10.1002/ajmg.a.36692. PMID: 25099136.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department Orthopaedics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
2. Professor, Department of Orthopaedics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
3. Junior Resident, Department of Orthopaedics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
4. Junior Resident, Department of Orthopaedics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
5. Undergraduate Student, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Shashank Yadav,
Junior Resident, Department Orthopaedics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha-442001, Maharashtra, India.
E-mail: shashankyadav0029@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Nov 29, 2025
- Manual Googling: Apr 04, 2026
- iThenticate Software: Apr 06, 2026 (1%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Nov 24, 2025**
Date of Peer Review: **Feb 01, 2026**
Date of Acceptance: **Apr 08, 2026**
Date of Publishing: **Jul 01, 2026**