U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Wallace SE, Wilcox WR. Camurati-Engelmann Disease. 2004 Jun 25 [Updated 2023 Aug 31]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Camurati-Engelmann Disease

Synonym: Progressive Diaphyseal Dysplasia, *TGFB1*-Related Diaphyseal Dysplasia Camurati-Engelmann

Stephanie E Wallace, MD[1] and William R Wilcox, MD, PhD[2]

Created: June 25, 2004; Updated: August 31, 2023.

Summary

Clinical characteristics

Camurati-Engelmann disease (CED) is characterized by hyperostosis of the long bones and the skull, proximal muscle weakness, limb pain, a wide-based, waddling gait, and joint contractures. Facial features such as macrocephaly, frontal bossing, enlargement of the mandible, proptosis, and cranial nerve impingement resulting in facial palsy are seen in severely affected individuals later in life.

Diagnosis/testing

The diagnosis of CED is established in a proband with the characteristic radiographic findings or (if radiographic findings are inconclusive) a heterozygous pathogenic variant in *TGFB1* identified by molecular genetic testing.

Management

Targeted therapy: Corticosteroid therapy as needed to control symptoms; losartan may be a helpful adjuvant therapy to minimize the need for steroids to control pain.

Supportive care: Management of muscle weakness and gait issues per physical medicine and rehabilitation specialists and physical therapist. Treatment of joint contractures and other musculoskeletal manifestations per orthopedist with experience in skeletal dysplasias; pain is also managed with analgesics, non-pharmacologic methods, and on occasion surgical treatment. Management of hearing loss per otolaryngologist; bilateral myringotomy can improve conductive hearing loss resulting from serous otitis. Treatment of ocular manifestations per ophthalmic subspecialist with low vision services as needed; craniectomy may be needed to reduce intracranial pressure and relieve symptoms in individuals with several cranial sclerosis. Adjustment of corticosteroids or losartan as needed for hyper- or hypotension; treatment with antihypertensives as needed; mobility assessment with adaptive devices and fall precautions.

Author Affiliations: 1 Division of Genetic Medicine, University of Washington, Seattle Children's Hospital, Seattle, Washington; Email: stephanie.wallace@seattlechildrens.org. 2 Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia; Email: william.wilcox@emory.edu.

Surveillance: Assess development of gross motor skills throughout childhood; assess for mobility issues, weakness, contractures, bone pain, and other musculoskeletal manifestations at each visit; serum ESR and bone scan as needed in those with acute bone pain to assess disease activity; evaluation of bone mineral density annually in those treated with corticosteroids; annual neurologic examination to assess for cranial nerve deficits and headaches; monitor for signs and symptoms of increased intracranial pressure at each visit; head and neck CT as needed in those with sclerosis of the skull base and neurologic symptoms to determine extent of disease and allow consideration of surgical treatment options; annual audiology evaluation with BAER and inner ear CT as needed; monitor linear growth and pubertal development at each visit throughout childhood; assess blood pressure at each visit; annual CBC.

Agents/circumstances to avoid: Excess phosphate.

Evaluation of relatives at risk: It is appropriate to evaluate relatives at risk in order to identify the diagnosis as early as possible, avoid potential misdiagnosis, and provide appropriate treatment for extremity pain.

Genetic counseling

CED is inherited in an autosomal dominant manner. Many individuals diagnosed with CED have an affected parent; some individuals diagnosed with CED may have the disorder as the result of a *de novo* *TGFB1* pathogenic variant. Each child of an individual with CED has a 50% chance of inheriting the *TGFB1* pathogenic variant. Once the *TGFB1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for CED are possible.

GeneReview Scope

The scope of this *GeneReview* encompasses Camurati-Engelmann disease (CED) and Ribbing disease. CED and Ribbing disease are both caused by pathogenic variants in *TGFB1* and represent phenotypic variations of the same disorder.

Diagnosis

No consensus clinical diagnostic criteria for Camurati-Engelmann disease have been published.

Suggestive Findings

Camurati-Engelmann disease (CED) **should be suspected** in individuals with the following clinical findings:

- Proximal muscle weakness
- Easy fatigability
- Bone pain primarily affecting the lower extremities
- Waddling gait

Establishing the Diagnosis

The clinical diagnosis of CED can be **established** in a proband with the characteristic radiographic findings or, if radiographic findings are inconclusive, a heterozygous pathogenic (or likely pathogenic) variant in *TGFB1* identified by molecular genetic testing (see Table 1).

Clinical Diagnosis

The clinical diagnosis is based on the following radiographic findings:

- **Long bones.** Hyperostosis of one or more of the long bones begins with the diaphyses and can progress to the metaphyses and rarely involves the epiphyses.

- Periosteal involvement results in uneven cortical thickening and increased bone diameter.
- Endosteal bony sclerosis can lead to a narrowed medullary canal.
- Hyperostosis is usually symmetric in the appendicular skeleton but in some instances is asymmetric.

- **Skull.** Hyperostosis begins at the base of the anterior and middle fossae and often includes the frontal bone [Wallace et al 2004].
- **Other.** Mild osteosclerosis is present in the posterior neural arch of the spine and parts of the flat bones that correspond to the diaphysis.

Molecular Diagnosis

The molecular diagnosis can be established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *TGFB1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *TGFB1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see **Option 1**), whereas comprehensive genomic testing does not (see **Option 2**).

Option 1

Single-gene testing. Sequence analysis of *TGFB1* is performed.

Note: CED is postulated to occur through a gain-of-function mechanism. Large intragenic deletions or duplications have not been reported in individuals with CED; testing for intragenic deletions or duplication is not indicated.

A multigene panel that includes *TGFB1* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of CED has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Camurati-Engelmann Disease

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TGFB1	Sequence analysis [3]	>90% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]
Unknown [7]	NA	

NA = not applicable
1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. The majority are missense variants in exon 4 leading to single amino acid substitutions in the encoded protein [Janssens et al 2000, Kinoshita et al 2000, Campos-Xavier et al 2001, Hecht et al 2001, Mumm et al 2001, Janssens et al 2003, Kinoshita et al 2004, Wallace et al 2004, Janssens et al 2006].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Large intragenic deletions or duplications have not been reported in individuals with CED.
7. The affected members of one family with clinical and radiographic features of CED did not share marker haplotypes at the *TGFB1* locus and had no sequence alterations in *TGFB1* exons 1 through 7; deletion/duplication analysis was not done on these individuals [Hecht et al 2001]. Several additional individuals with clinical and radiographic features of CED have not had *TGFB1* pathogenic variants identified, implying genetic locus heterogeneity [Authors, personal observation].

Clinical Characteristics

Clinical Description

Individuals with Camurati-Engelmann disease (CED) present with proximal muscle weakness, poor muscular development, a wide-based, waddling gait, easy fatigability, bone pain, and headaches. The average age of onset of symptoms in the 306 reported individuals is 13.4 years [Carlson et al 2010] with a range of onset from birth to age 76 years [Wallace et al 2004].

Table 2. Camurati-Engelmann Disease: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Proximal muscle weakness	62%-67%	
Wide-based, waddling gait	48%-79%	
Easy fatigability	54%	
Bone pain	68%-100%	
Hearing loss	19%-54%	Sensorineural &/or conductive
Headaches	25%	

Wallace et al [2004], Carlson et al [2010], Li et al [2022], Liang et al [2022]

Musculoskeletal. Decreased muscle mass and weakness are most apparent in the proximal lower limbs, resulting in difficulty when rising from a sitting position. A wide-based, waddling gait is common. Delayed onset of walking has been reported [Kim et al 2018, Mwasamwaja et al 2018]. Joint contractures occur in 43% of individuals. Marfanoid body habitus is described in some affected individuals, with reduction of muscle mass and subcutaneous tissue resulting in low body mass index in some individuals [Wallace et al 2004, Janssens et al

2006, Van Hul et al 2019]. Musculoskeletal involvement can lead to varying degrees of lumbar lordosis, kyphosis, scoliosis, coxa valga, radial head dislocation, genu valgum, hallux valgus, and flat feet [Yuldashev et al 2017].

Bone pain is reported in the majority of affected individuals [Wallace et al 2004, Janssens et al 2006, Liang et al 2022]. The reported severity of bone pain ranged from mild (not requiring any treatment) to severe (requiring narcotic analgesics) [Yuldashev et al 2017]. The pain is described as constant, aching, and most intense in the lower limbs. Pain often increases with activity, stress, and cold weather. Many individuals have intermittent episodes of severe pain and incapacitation. Bone pain has resulted in limited ambulation in some individuals. The enlarged bone shafts can also be palpable and tender on examination; 52% of affected individuals report bone tenderness with palpation [Wallace et al 2004]. Intermittent limb swelling, erythema, and warmth also occur. Corticosteroid treatment has been reported to reduce pain and weakness and improve gait, exercise tolerance, and flexion contractures in several individuals [Lindstrom 1974, Baş et al 1999, Wallace et al 2004, Mwasamwaja et al 2018, Liang et al 2022]. Losartan alone or in combination with corticosteroids was reported to reduce bone pain and increase physical activity [Ayyavoo et al 2014, Simsek-Kiper et al 2014, Kim et al 2018, Abdulla 2019, Cui et al 2022]. The severity of bone pain may decrease in adulthood [Hughes et al 2019].

Although bone mineral density measured at the hip and femoral neck are increased in individuals with CED, bone strength measured by bone impact microindentation in three sibs with CED was below normal. Because of the small sample size, the difference in bone strength was not statistically significant [Herrera et al 2017]. Increased susceptibility to fracture has not been reported. Healing of fractures, when they occur, may be delayed [Wallace et al 2004].

Neurologic. Sclerosis of the cranial nerve foramina can lead to direct nerve compression or neurovascular compromise. Cranial nerve deficits occur in 38% of affected individuals. The most common deficits are hearing loss, vision problems, and facial paralysis.

Approximately 19%-54% of individuals with CED have conductive and/or sensorineural hearing loss [Carlson et al 2010, Liang et al 2022]. Conductive loss can be caused by narrowing of the external auditory meatus, bony encroachment of the ossicles, or narrowing of the oval and round windows. Sensorineural hearing loss is caused by narrowing of the internal auditory canal and compression of the cochlear nerve and/or vasculature. Sensorineural hearing loss can also occur with attempted decompression of the facial nerves.

Vestibulopathy including tinnitus and vertigo have also been reported in several individuals [Carlson et al 2010, Kim et al 2018].

Involvement of the orbit has led to blurred vision, proptosis, papilledema, epiphora, glaucoma, subluxation of the globe, and retinal detachment [Carlson et al 2010, Popiela & Austin 2015, Kim et al 2018].

Facial paralysis has been successfully treated by surgical decompression of the facial nerve in one affected individual [Achahbar et al 2021].

Calvarial hyperostosis can lead to increased intracranial pressure, chronic headaches that can be severe, and frontal bossing. Chronic intracranial hypertension led to a bone defect and meningoencephalocele in one individual at age 57 years [Yanagihara et al 2022]. Recurrent cranial hyperostosis following surgical decompression can occur [Wong et al 2017].

Rarely, clonus [Neuhauser et al 1948], sensory loss, slurred speech, dysphagia, cerebellar ataxia, and bowel and bladder incontinence are reported [Carlson et al 2010].

Corticosteroids may delay bone hyperostosis and prevent or delay the onset of skull involvement. Although histologic studies following steroid therapy showed increased bone resorption and secondary remodeling with increased osteoblast activity and decreased lamellar bone deposition, several authors reported no regression of sclerosis on radiographic evaluation [Verbruggen et al 1985] or on scintigraphic evaluation [Baş et al 1999].

Lindstrom [1974] and Baş et al [1999] reported diminished sclerosis on radiographs following steroid therapy. Verbruggen et al [1985] and Inaoka et al [2001] reported reduced radioactivity on bone scintigraphy.

Endocrine manifestations. Hypopituitarism has been described in several individuals, resulting in short stature, delayed pubertal development, and hypocortisolism [Yuldashev et al 2017, Li et al 2022]. Hypopituitarism has been attributed to skull base osteosclerosis resulting in a small sella and/or pituitary compression due to intracranial hypertension [Das et al 2021]. In addition, hypopituitarism may be secondary to direct effects of TGFB1 on the pituitary gland. Hypogonadism and lack of pubertal development has also been attributed to reduced adipose tissue and/or direct effects of TGFB1 on the gonads [Das et al 2021]. Combination corticosteroid therapy and losartan led to initiation of pubertal development in a female age 18 years [Cui et al 2022]. Hypothyroidism is also rarely described as a result of pituitary effects or autoimmune hypothyroidism [Das et al 2021].

Facial features. Children with CED do not typically have recognizable changes to their facial features. In older individuals who are severely affected, osteosclerosis of the skull can lead to macrocephaly, frontal bossing, enlargement of the mandible, proptosis, and cranial nerve impingement resulting in facial palsy.

Less common manifestations in individuals with CED include anemia (hypothesized to be caused by a narrowed medullary cavity), hepatosplenomegaly, atrophic skin, hyperhidrosis of the hands and feet, delayed dental eruption, and extensive dental caries.

Ribbing disease, an osteosclerotic disease of the long bones that is radiographically indistinguishable from CED and usually presents with bone pain after puberty [Makita et al 2000], is now known to be caused by pathogenic variants in *TGFB1* [Janssens et al 2006]. Thus, CED and Ribbing disease represent phenotypic variations of the same disorder.

Other. Osteoblastoma of the distal radius and enchondroma of the fifth finger have each been reported in one individual with clinical and radiographic diagnosis of CED and no *TGFB1* pathogenic variant identified [Nagasawa et al 2010, Yonezawa et al 2021].

The authors are aware of one teenager with CED who died following dissection of a dilated ascending aorta [Authors, personal communication]. To date, it is unknown if dilatation of the aorta is a rare manifestation of CED. The authors are unaware of any additional individuals with aortic disease. Because the mechanism of CED involves increased TGFB1 signaling, also found in Marfan syndrome and Loeys-Dietz syndrome, incidence of aortic disease in those with CED should continue to be reassessed. At this time no recommendations for routine evaluation of the aorta can be made.

Pregnancy. One individual who experienced relief with steroids also experienced decreased bone pain and improved muscle strength while pregnant, which allowed discontinuation of her steroid therapy. Scintigraphic bone imaging with methylene diphosphate (MDP) a few hours after delivery of her second child showed decreased uptake compared to imaging prior to pregnancy and six weeks postpartum.

Genotype-Phenotype Correlations

No known correlation exists between the nature of the *TGFB1* pathogenic variants and the severity of the clinical or radiographic manifestations [Campos-Xavier et al 2001].

Penetrance

Some obligate heterozygotes with an identified *TGFB1* pathogenic variant have had normal radiographs [Wallace et al 2004]; an exact penetrance figure is not known.

Nomenclature

Engelmann described the second reported occurrence of CED in 1929 as "osteopathic hyperostotica (sclerotisans) multiplex infantilis."

The terms "Engelmann disease" and "diaphyseal dysplasia" were commonly used until Neuhauser et al [1948] coined the term "progressive diaphyseal dysplasia."

Gulledge & White [1951] suggested the term "progressive diaphyseal hyperostosis," which was not widely used.

CED is referred to as "*TGFB1*-related diaphyseal dysplasia Camurati-Engelmann" in the 2023 revision of the Nosology and Classification of Genetic Skeletal Disorders [Unger et al 2023].

Prevalence

The prevalence is unknown. More than 300 affected individuals have been reported.

Genetically Related (Allelic) Disorders

Biallelic loss-of-function variants in *TGFB1* have been reported in several individuals with inflammatory bowel disease, immunodeficiency, and encephalopathy (OMIM 618213).

Differential Diagnosis

Few disorders share the clinical and radiographic findings of Camurati-Engelmann disease (CED). The correct diagnosis is made by physical examination and skeletal survey.

Table 3. Genes of Interest in the Differential Diagnosis of Camurati-Engelmann Disease

Gene	Disorder	MOI	Features Overlapping w/CED	Features Distinguishing From CED
COL1A1	Caffey disease, *COL1A1*-related	AD	Bone pain, hyperostosis of diaphyses of long bones	Hyperostosis resolves spontaneously over time; additional features of fever, joint laxity, & skin hyperextensibility in Caffey disease.
FAM111A	Kenny-Caffey syndrome, dominant, *FAM111A*-related (*FAM111A*-KCS) (See *FAM111A*-Related Skeletal Dysplasias.)	AD	Sclerosis of long bones, cortical thickening, medullary stenosis	In *FAM111A*-KCS: hypocalcemia, hypoparathyroidism, & delayed fontanelle closure
LRP5	Osteosclerosis, *LRP5*-related (OMIM 144750)	AD	Diaphyseal sclerosis (endosteal), cranial nerve involvement in some	In *LRP5*-related osteosclerosis: wide, deep mandible w/↑ gonial angle (distinct from enlarged mandible found only occasionally in CED)
LRP6	Camurati-Engelmann-like disease, *LRP6*-related [1]	AD	Bone pain, periosteal & endosteal diaphyseal sclerosis of long bones	In *LRP6*-related Camurati-Engelmann-like disease: diaphyseal sclerosis of metacarpals; cranial sclerosis spares the cranial vault

Table 3. continued from previous page.

Gene	Disorder	MOI	Features Overlapping w/CED	Features Distinguishing From CED
SOST	Craniodiaphyseal dysplasia, *SOST*-related (*SOST*-CDD) (OMIM 122860) [2]	AD	Diaphyseal sclerosis & cranial hyperostosis	Cranial involvement in CED is milder & rarely results in frontal bossing & proptosis. Choanal stenosis is significant in *SOST*-CDD. Sclerosis of long bones in CDD is restricted to diaphysis, whereas in CED, metaphyses can also be affected.
	SOST-related sclerosing bone dysplasias (sclerosteosis, *SOST*-related, & endosteal hyperostosis, van Buchem type, *SOST*-related)	AR	Cranial hyperostosis, cranial nerve involvement, diaphyseal sclerosis	In *SOST*-related sclerosing bone dysplasias: syndactyly & dysplastic or absent nails
SP7	Craniodiaphyseal dysplasia, *SP7*-related (*SP7*-CDD) [3]	AR	Cranial hyperostosis, diaphyseal sclerosis	In *SP7*-CDD: undertubulation of metacarpals, phalanges, & long bones; broad ribs & clavicles
TBXAS1	Hematodiaphyseal dysplasia Ghosal, *TBXAS1*-related (OMIM 231095)	AR	Diaphyseal sclerosis	Severe anemia; leukopenia & thrombocytopenia in *TBXAS1*-related hematodiaphyseal dysplasia Ghosal
TNFRSF11B	Osteoectasia w/hyperphosphatasia (juvenile Paget disease), *TNFRSF11B*-related (OMIM 239000)	AR	Cranial hyperostosis, sensorineural hearing loss, sclerosis of long bones	In juvenile Paget disease: predisposition to fractures & bowing of long bones

AD = autosomal dominant; AR = autosomal recessive; CED = Camurati-Engelmann disease; MOI = mode of inheritance
1. Pickering et al [2021]
2. SOST-related craniodiaphyseal dysplasia has been reported in two affected children [Kim et al 2011]. Since this report no other cases have been published.
3. Hendrickx et al [2023]

Other disorders that may confused with CED include rheumatoid arthritis [Alamlih et al 2018], sarcoidosis [Nagra et al 2023], muscular dystrophy, and polymyositis [Wallace et al 2004].

Management

No clinical practice guidelines for Camurati-Engelmann disease (CED) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with CED, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Camurati-Engelmann Disease: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval to assess for weakness, contractures, bone pain, & other musculoskeletal manifestations	To incl assessment of: • Gross motor skills • Mobility, ADL, & need for adaptive devices • Need for PT
	Complete skeletal survey	Use of whole-body MRI to identify affected areas has been described. [1]
	• Serum ESR • Bone scan (scintigraphy) exam	In those w/acute bone pain to assess disease activity

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Neurologic exam to assess for cranial nerve deficits & headaches	In those w/sclerosis of skull base & neurologic symptoms, consider head & neck CT to determine extent of disease & allow consideration of surgical treatment options.
Hearing	Audiology eval for conduction &/or sensorineural hearing deficits	In those w/hearing loss: BAER & CT w/fine cuts through inner ear
Eyes	Ophthalmology exam to assess for blurred vision, proptosis, papilledema, epiphora, & glaucoma	
Endocrine	Assess pubertal development & for other clinical manifestations of hypopituitarism.	
Cardiac	Blood pressure	Baseline blood pressure is needed in those considering treatment w/losartan.
Hematologic	CBC	To assess for anemia in those w/significant endosteal involvement
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of CED to facilitate medical & personal decision making

ADL = activities of daily living; BAER = brain stem auditory evoked response; CBC = complete blood count; CED = Camurati-Engelmann disease; ESR = erythrocyte sedimentation rate; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Corrêa et al [2020]

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for CED.

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Corticosteroids may relieve many of the symptoms of CED. Several investigators report success with corticosteroid treatment in reducing pain and weakness; improving gait, exercise tolerance, and flexion contractures; correcting anemia and hepatosplenomegaly; and preventing or delaying bone hyperostosis, including skull involvement and cranial nerve impingement [Lindstrom 1974, Baş et al 1999, Wallace et al 2004, Mwasamwaja et al 2018].

Individuals with severe symptoms can be treated with a bolus of prednisolone 1.0-2.0 mg/kg/day followed by rapid tapering to the lowest alternate-day dose tolerated. Less symptomatic individuals can be started on 0.5-1.0 mg/kg every other day. Some individuals may be able to discontinue steroid therapy during quiescent periods. Higher-dose steroids may help with acute pain crises.

After initiating corticosteroids, affected individuals should be followed monthly, with efforts to taper the steroids to the lowest tolerated dose to reduce the risk of osteoporosis and compression fractures of the spine. Blood pressure should be monitored at each visit, as hypertension can develop following the initiation of corticosteroid therapy.

Losartan. Reduced bone pain and increased physical activity have been reported in several individuals treated with losartan [Ayyavoo et al 2014, Simsek-Kiper et al 2014, Kim et al 2018, Abdulla 2019, Agarwal et al 2021]. Losartan has been shown to downregulate transforming growth factor beta-1 signaling.

Combination corticosteroid therapy and losartan led to decreased bone pain and initiation of pubertal development in a female age 18 years [Cui et al 2022]. Treatment with losartan has not improved bone pain in some individuals [Yuldashev et al 2017, Combier et al 2018].

Long-term follow-up studies are needed to further evaluate the benefits and risk of corticosteroid therapy, losartan, and combination therapy.

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Camurati-Engelmann Disease: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Weakness / Gait issues	Physical medicine, rehab, & PT	Consider need for positioning & mobility devices, disability parking placard.
Joint contractures / Other musculoskeletal manifestations	Treatment per orthopedist w/experience in skeletal dysplasias	
Bone pain	Treatment options: • Corticosteroids • Losartan • Analgesic medications • Non-pharmacologic pain control methods • Surgical treatment (intramedullary reaming)	• See Targeted Therapy for discussion of corticosteroids & losartan. • Successful surgical treatment of persistent bone pain has been described. [1]
	Additional treatment options: • Pain relief from intranasal calcitonin was reported in 1 person. [2] • Infliximab treatment alleviated pain in 1 person who did not respond to corticosteroids. [3]	
Hearing loss	• Mgmt per otolaryngologist • Eval should incl BAER & CT w/fine cuts through inner ear. • Bilateral myringotomy can improve conductive hearing loss resulting from serous otitis in persons w/CED. • Cochlear implantation improved hearing in 1 person w/conductive hearing loss & patent internal auditory canals. [4] • See also Hereditary Deafness and Hearing Loss Overview.	• Reports of successful treatment of hearing loss are rare. Surgical decompression of internal auditory canals can improve hearing. However, reported results are mixed. [5] The skull hyperostosis is progressive, & cranial nerve compression often recurs. • General contraindications for cochlear implants incl narrowed internal auditory canal & absence of functioning 8th cranial nerve, both of which can occur in CED.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Ocular manifestations	Ophthalmic subspecialist to manage complex findings due to orbit involvement	
	Low vision services	• Children: through early intervention programs &/or school district • Adults: low vision clinic &/or community vision services / OT / mobility services
Headaches / Increased ICP	Treatment options: • Craniectomy • See Targeted Therapy (corticosteroids &/or losartan).	Craniectomy relieved ↑ ICP & headaches. [5] Recurrent cranial hyperostosis w/resultant ↑ ICP has been managed by radical craniectomy w/ titanium mesh cranioplasties. [6]
Hypertension	• Adjust corticosteroid dose as needed. • Standard treatments for hypertension as needed.	Hypertension may occur in those treated w/ corticosteroid therapy.
Hypotension	• Adjust losartan dose as needed. • Assess mobility, need for adaptive devices, & fall precautions.	Hypotension may occur in those treated w/ losartan.

BAER = brain stem auditory evoked response; CED = Camurati-Engelmann disease; ICP = intracranial pressure; OT = occupational therapy; PT = physical therapy

1. Oztürkmen & Karamehmetoğlu [2011], Saboya et al [2021]
2. Trombetti et al [2012]
3. Moreira et al [2017]
4. Friedland et al [2000]
5. Carlson et al [2010]
6. Wong et al [2017]

Potential treatments to consider with caution

- **Bisphosphonates.** Pamidronate did not improve symptoms in four individuals [Inaoka et al 2001, Janssens et al 2006]. Clodronate infusion caused increased bone pain in one individual with CED and no improvement in another individual reported by Castro et al [2005]. Decreased bone pain, decreased size of hyperostotic lesions in the long bones, improved weight gain, and improved ambulation were reported in two individuals treated with zolendronic acid infusions [Baroncelli et al 2017]. One adult had immediate bone pain relief after a single intravenous dose of zolendronic acid [Klemm et al 2023].

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. Camurati-Engelmann Disease: Recommended Surveillance

System/Concern	Evaluation	Frequency
Musculoskeletal	Assess gross motor skills.	At each visit throughout childhood
	Assess for mobility issues, weakness, contractures, bone pain, & other musculoskeletal manifestations.	At each visit
	• Serum ESR • Bone scan (bone scintigraphy) exam	As needed in those w/acute bone pain to assess disease activity
	Eval of bone mineral density	• Annually in those treated w/corticosteroids • CED does not appear to cause ↑ in spine density; therefore, steroid therapy could lead to osteoporosis of spine [Authors, personal observation].
Neurologic	• Neurologic exam to assess for cranial nerve deficits & headaches • Monitor for signs & symptoms of ↑ ICP.	Annually
	Head & neck CT	As needed in those w/sclerosis of skull base & neurologic symptoms to determine extent of disease & allow consideration of surgical treatment options
Hearing	Audiology eval for conduction &/or sensorineural hearing deficits	Annually
	BAER & CT w/fine cuts through inner ear	As needed in those w/ hearing loss
Eyes	Ophthalmology exam to assess for blurred vision, proptosis, papilledema, epiphora, & glaucoma	Annually
Endocrine	Monitor linear growth & pubertal development.	At each visit throughout childhood
Cardiac	Blood pressure	At each visit
Hematologic	CBC	Annually

BAER = brain stem auditory evoked response; CBC = complete blood count; CED = Camurati-Engelmann disease; ESR = erythrocyte sedimentation rate; ICP = intracranial pressure

Agents/Circumstances to Avoid

Excess phosphate. Treatment with cellulose phosphate led to worsening hypocalcemia and proximal myopathy in one individual.

Evaluation of Relatives at Risk

It is appropriate to evaluate relatives at risk in order to identify the diagnosis as early as possible, avoid potential misdiagnosis, and provide appropriate treatment for extremity pain. Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- Radiographic evaluation for hyperostosis if the pathogenic variant in the family is not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Camurati-Engelmann disease (CED) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with CED have an affected parent.
- Some individuals diagnosed with CED may have the disorder as the result of a *de novo* *TGFB1* pathogenic variant. The proportion of individuals with CED caused by a *de novo* pathogenic variant is unknown.
- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with CED may appear to be negative because of failure to recognize the disorder in family members, early death of a parent before the onset of symptoms, or reduced penetrance in a parent. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation (radiographs) of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents.

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Because of reduced penetrance, some individuals who inherit a *TGFB1* pathogenic variant will not have manifestations. The exact penetrance is unknown.
- CED is associated with significant intrafamilial phenotypic variability; the severity of disease manifestations in affected sibs is impossible to predict [Hughes et al 2019].
- If the proband has a known *TGFB1* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with CED has a 50% chance of inheriting the *TGFB1* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *TGFB1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *TGFB1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for CED are possible. Because of reduced penetrance, results of prenatal testing may not be useful in accurately predicting age of onset, severity, type of symptoms, or rate of progression.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **Face Equality International**
  United Kingdom
  faceequalityinternational.org
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org

- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Camurati-Engelmann Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TGFB1	19q13.2	Transforming growth factor beta-1 proprotein	TGFB1 homepage	TGFB1	TGFB1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Camurati-Engelmann Disease (View All in OMIM)

131300	CAMURATI-ENGELMANN DISEASE; CAEND
190180	TRANSFORMING GROWTH FACTOR, BETA-1; TGFB1
601477	RIBBING DISEASE

Molecular Pathogenesis

TGFB1 encodes transforming growth factor beta-1 (TGFB1), which is synthesized as a large precursor molecule. TGFB1 preprotein contains a signal peptide of 29 amino acids that is proteolytically cleaved. TGFB1 is further cleaved after amino acid 278 to form latency-associated peptide (LAP) and active TGFB1. LAP dimerizes with interchain disulfide links at Cys223 and Cys225. TGFB1 can be secreted as an inactive small latent complex that consists of a mature TGFB1 homodimer non-covalently associated with an LAP homodimer at LAP residues Ile^{53}-Leu^{59}. LAP shields the type II receptor binding sites in the mature TGFB1. Most cells secrete TGFB1 as a large latent complex (LLC) of TGFB1/LAP covalently bound between Cys^{33} in the LAP chains and latent TGFB1-binding protein (LTBP). LTBPs facilitate TGFB1 folding, secretion, and possibly targeting to the extracellular matrix. Activation of the LLC occurs via the N-terminal domain of LTBP binding to the extracellular matrix.

The majority of pathogenic variants in individuals with Camurati-Engelmann disease (CED) result in single amino acid substitutions in the carboxy terminus of LAP. The substitutions are near the site of interchain disulfide bonds between the LAP homodimers. These pathogenic variants disrupt dimerization of LAP and binding to active TGFB1 [Walton et al 2010], leading to increased active TGFB1 release from the cell. p.Arg218His mutated fibroblasts from individuals with CED showed increased active TGFB1 in the cell media compared to normal fibroblasts [Saito & Kinoshita 2001]. In vitro analysis of p.Arg218Cys, p.His222Asp, and p.Cys225Arg mutated constructs also showed increased active TGFB1 in the medium of transfected cells. In contrast, the p.Leu11_Leu13dup and p.Tyr81His pathogenic variants caused a decrease in the amount of TGFB1 secreted. However, in a luciferase reporter assay specific for TGFB1-induced transcriptional response, the mutated cells showed increased luciferase activity, suggesting intracellular activation of the receptor [Janssens et al 2003]. *TGFB1* pathogenic variants may alter bone remodeling processes in part by aberrant activation of Rho GTPases [Chen et al 2022].

Mechanism of disease causation. Gain of function

Table 7. *TGFB1* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_000660.7 NP_000651.3	c.30_38dupGCTGCTGCT	p.Leu11_Leu13dup	See Molecular Pathogenesis.
	c.241T>C	p.Tyr81His	
	c.652C>T	p.Arg218Cys	Common pathogenic variant; identified in ~40% of individuals w/CED. [1]
	c.653G>A	p.Arg218His	Common pathogenic variants; identified in ~35% of individuals w/CED. [1]
	c.673T>C	p.Cys225Arg	
	c.664C>G	p.His222Asp	See Molecular Pathogenesis.

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Janssens et al [2000], Kinoshita et al [2000], Campos-Xavier et al [2001], Hecht et al [2001], Mumm et al [2001], Janssens et al [2003], Kinoshita et al [2004], Wallace et al [2004], Janssens et al [2006], Van Hul et al [2019]

Chapter Notes

Acknowledgments

The authors would like to thank all of the individuals with Camurati-Engelmann disease and their families for contributing to the understanding of this disorder.

Revision History

- 31 August 2023 (sw) Comprehensive updated posted live
- 12 October 2017 (ha) Comprehensive update posted live
- 5 March 2015 (me) Comprehensive update posted live
- 6 December 2012 (me) Comprehensive update posted live
- 1 June 2010 (me) Comprehensive update posted live
- 16 August 2006 (me) Comprehensive update posted live
- 25 June 2004 (me) Review posted live
- 18 March 2004 (sw) Original submission

References

Literature Cited

Abdulla MC. Camurati-Engelmann disease with good treatment response to losartan. Indian J Nucl Med. 2019;34:223-5. PubMed PMID: 31293304.

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:CASE2039. PubMed PMID: 36131584.

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. 2021;8:54-7. PubMed PMID: 35415233.

Alamlih L, Alkahlout M, Siam A, Alam S, Al-Allaf AW. Seropositive rheumatoid arthritis with very unusual X-ray findings. Eur J Case Rep Intern Med. 2018;5:000883. PubMed PMID: 30756048.

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;99:3978-82. PubMed PMID: 25140400.

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;8:294-302. PubMed PMID: 29230158.

Baş F, Darendeliler F, Petorak I, Sadikoglu B, Bilir A, Bundak R, Saka N, Gunoz H. Deflazacort treatment in progressive diaphyseal dysplasia (Camurati-Engelmann disease). J Paediatr Child Health. 1999;35:401-5. PubMed PMID: 10457303.

Campos-Xavier B, Saraiva JM, Savarirayan R, Verloes A, Feingold J, Faivre L, Munnich A, Le Merrer M, Cormier-Daire V. Phenotypic variability at the TGF-beta1 locus in Camurati-Engelmann disease. Hum Genet. 2001;109:653-8. PubMed PMID: 11810278.

Carlson ML, Beatty CW, Neff BA, Link MJ, Driscoll CL. Skull base manifestations of Camurati-Engelmann disease. Arch Otolaryngol Head Neck Surg. 2010;136:566-75. PubMed PMID: 20566907.

Castro GR, Appenzeller S, Marques-Neto JF, Bertolo MB, Samara AM, Coimbra I. Camurati-Engelmann disease: failure of response to bisphosphonates: report of two cases. Clin Rheumatol. 2005;24:398-401. PubMed PMID: 15660289.

Chen Q, Yao Y, Chen K, Chen X, Li B, Li R, Mo L, Hu W, Zhang M, Wang Z, Wu Y, Wu Y, Liu F. Aberrant activation of TGF-β1 induces high bone turnover via Rho GTPases-mediated cytoskeletal remodeling in Camurati-Engelmann disease. Front Endocrinol (Lausanne). 2022;13:913979. PubMed PMID: 36325441.

Combier A, Palazzo E, Forien M, Gardette A, Dieudé P. Failure of conventional treatment and losartan in Camurati-Engelmann disease: A case report. Joint Bone Spine. 2018;85:649-50. PubMed PMID: 29452301.

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:e10357. PubMed PMID: 32258971.

Cui L, Li Q, Guan W, Yu W, Li X, Xia W, Jiang Y. 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 (Lausanne). 2022;13:882144. PubMed PMID: 35784539.

Das L, Dhiman V, Dutta P, Sood A, Prakash M, Kaur S, Steenackers E, Hendrickx G, Dayal D, Van Hul W, Bhadada SK. Camurati-Engelmann disease complicated by hypopituitarism: management challenges and literature review of outcomes with bisphosphonates. AACE Clin Case Rep. 2021;8:58-64. PubMed PMID: 35415221.

Friedland DR, Wackym PA, Rhee JS, Finn MS. Cochlear implantation for auditory rehabilitation in Camurati-Engelmann disease. Ann Otol Rhinol Laryngol. 2000;109:160-2. PubMed PMID: 10685567.

Gulledge WH, White JW. Englemann's disease (progressive diaphyseal hyperostosis); report of a case. J Bone Joint Surg Am. 1951;33-A:793-7. PubMed PMID: 14850520.

Hecht JT, Blanton SH, Broussard S, Scott A, Rhoades Hall C, Milunsky JM. Evidence for locus heterogeneity in the Camurati-Engelmann (DPD1) Syndrome. Clin Genet. 2001;59:198-200. PubMed PMID: 11260231.

Hendrickx G, Boudin E, Steenackers E, Collet C, Mortier GR, Geneviève D, Van Hul W. A recessive form of craniodiaphyseal dysplasia caused by a homozygous missense variant in SP7/Osterix. Bone. 2023;167:116633. PubMed PMID: 36436818.

Herrera S, Soriano R,Nogués X, Güerri-Fernandez R, Grinberg D, García-Giralt N, Martínez-Gil N, Castejón S, González-Lizarán A, Balcells S, Diez-Perez A. Discrepancy between bone density and bone material strength

index in three siblings with Camurati-Engelmann disease. Osteoporos Int. 2017;28:3489-93. PubMed PMID: 28842728.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Hughes P, Hassan I, Que L, Mead P, Lee JH, Love DR, Prosser DO, Cundy T. Observations on the natural history of Camurati-Engelmann disease. J Bone Miner Res. 2019;34:875-82. PubMed PMID: 30690794.

Inaoka T, Shuke N, Sato J, Ishikawa Y, Takahashi K, Aburano T, Makita Y. Scintigraphic evaluation of pamidronate and corticosteroid therapy in a patient with progressive diaphyseal dysplasia (Camurati-Engelmann disease). Clin Nucl Med. 2001;26:680-2. PubMed PMID: 11452173.

Janssens K, Gershoni-Baruch R, Guanabens N, Migone N, Ralston S, Bonduelle M, Lissens W, Van Maldergem L, Vanhoenacker F, Verbruggen L, Van Hul W. Mutations in the gene encoding the latency-associated peptide of TGF-beta 1 cause Camurati-Engelmann disease. Nat Genet. 2000;26:273-5. PubMed PMID: 11062463.

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;278:7718-24. PubMed PMID: 12493741.

Janssens K, Vanhoenacker F, Bonduelle M, Verbruggen L, Van Maldergem L, Ralston S, Guanabens N, Migone N, Wientroub S, Divizia MT, Bergmann C, Bennett C, Simsek S, Melancon S, Cundy T, Van Hul W. 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. PubMed PMID: 15894597.

Kim SJ, Bieganski T, Sohn YB, Kozlowski K, Semënov M, Okamoto N, Kim CH, Ko AR, Ahn GH, Choi YL, Park SW, Ki CS, Kim OH, Nishimura G, Unger S, Superti-Furga A, Jin DK. Identification of signal peptide domain SOST mutations in autosomal dominant craniodiaphyseal dysplasia. Hum Genet. 2011;129:497–502. PubMed PMID: 21221996.

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:e0309. PubMed PMID: 29620655.

Kinoshita A, Fukumaki Y, Shirahama S, Miyahara A, Nishimura G, Haga N, Namba A, Ueda H, Hayashi H, Ikegawa S, Seidel J, Niikawa N, Yoshiura K. TGFB1 mutations in four new families with Camurati-Engelmann disease: Confirmation of independently arising LAP-domain-specific mutations. Am J Med Genet. 2004;127A:104-7. PubMed PMID: 15103729.

Kinoshita A, Saito T, Tomita H, Makita Y, Yoshida K, Ghadami M, Yamada K, Kondo S, Ikegawa S, Nishimura G, Fukushima Y, Nakagomi T, Saito H, Sugimoto T, Kamegaya M, Hisa K, Murray JC, Taniguchi N, Niikawa N, Yoshiura K. Domain-specific mutations in TGFB1 result in Camurati-Engelmann disease. Nat Genet. 2000;26:19-20. PubMed PMID: 10973241.

Klemm P, Aykara I, Lange U. Camurati-Engelmann disease: a case-based review about an ultrarare bone dysplasia. Eur J Rheumatol. 2023;10:34-8. PubMed PMID: 36880809.

Li Q, Zhao Z, Wu B, Pang Q, Cui L, Zhang L, Jiang Y, Wang O, Li M, Xing X, Hu Y, Yu W, Meng X, Jiajue R, Xia W. Alteration of bone density, microarchitecture, and strength in patients with Camurati-Engelmann disease: assessed by HR-pQCT. J Bone Miner Res. 2022;37:78-86. PubMed PMID: 34490910.

Liang H, Jiajue R, Qi W, Liu W, Chi Y, Jiang Y, Wang O, Li M, Xing X, Xia W. Clinical characteristics and the influence of rs1800470 in patients with Camurati-Engelmann disease. Front Endocrinol (Lausanne). 2022;13:1041061. PubMed PMID: 36339419.

Lindstrom JA. Diaphyseal dysplasia (Engelmann) treated with corticosteroids. Birth Defects Orig Artic Ser. 1974;10:504-7. PubMed PMID: 4461085.

Makita Y, Nishimura G, Ikegawa S, Ishii T, Ito Y, Okuno A. Intrafamilial phenotypic variability in Engelmann disease (ED): are ED and Ribbing disease the same entity? Am J Med Genet. 2000;91:153-6. PubMed PMID: 10748417.

Moreira S, Cunha B, Jesus NP, Santos L. Pain improvement in Camurati-Engelmann disease after anti-TNFα therapy. Case Reports BMJ Case Rep. 2017;2017:bcr2017221760.

Mumm SR, Obrecht S, Podgornik MN, Whyte MP. Camurati-Engelmann disease: new mutations in the latency-associated peptide of the transforming growth factor B-1 gene. Am J Hum Genet. 2001;69S:593.

Mwasamwaja AO, Mkwizu EW, Shao ER, Kalambo CF, Lyaruu I, Hamel BC. Camurati-Engelmann disease: a case report from sub-Saharan Africa. Oxford Medical Case Reports. 2018;2018:omy036. PubMed PMID: 30034812.

Nagasawa H, Okada K, Nanjo H, Sasaki H, Chida S, Shimada Y. Unusual association between enchondroma and Camurati-Engelmann disease: a case report. Ups J Med Sci. 2010;115:157-60. PubMed PMID: 19943817.

Nagra D, Russell MD, Alveyn E, Birring SS, Elias D, Balachandran S, Galloway JB. Diagnosing Camurati-Engelmann disease-the age of whole exome sequencing. Rheumatology (Oxford). 2023;62:e221-e222. PubMed PMID: 36519831.

Neuhauser EBD, Schwachman H, Wittenborg M, Cohen J. Progressive diaphyseal dysplasia. Radiology. 1948;51:11-22. PubMed PMID: 18869144.

Oztürkmen Y, Karamehmetoğlu M. Ribbing disease: a case report and literature review. Acta Orthop Traumatol Turc. 2011;45:58-65. PubMed PMID: 21478664.

Pickering ME, Ltaief-Boudrigua A, Feurer E, Collet C, Chapurlat R. A new LRP6 variant and Camurati-Engelmann-like disease. Bone. 2021;143:115706. PubMed PMID: 33164853.

Popiela M, Austin M. Bilateral papilloedema in Camurati-Engelmann disease. BMJ Case Rep. 2015;2015:bcr2014207348. PubMed PMID: 26286906.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126-33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Saboya F, Medina A, Cadavid S, Fuentes R, Jiménez-Canizales CE. Surgery treatment of an adult patient with Camurati-Engelmann disease: a case report. Case Reports JBJS Case Connect. 2021;11.

Saito T, Kinoshita A, Yoshiura Ki, Makita Y, Wakui K, Honke K, Niikawa N, Taniguchi N. Domain-specific mutations of a transforming growth factor (TGF)-beta 1 latency-associated peptide cause Camurati-Engelmann disease because of the formation of a constitutively active form of TGF-beta 1. J Biol Chem. 2001;276:11469-72. PubMed PMID: 11278244.

Simsek-Kiper PO, Dikoglu E, Campos-Xavier B, Utine GE, Bonafe L, Unger S, Boduroglu K, Superti-Furga A. 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:2667-71. PubMed PMID: 25099136.

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;41:75-7. PubMed PMID: 22044122.

Unger S, Ferreira CR, Mortier GR, Ali H, Bertola DR, Calder A, Cohn DH, Cormier-Daire V, Girisha KM, Hall C, Krakow D, Makitie O, Mundlos S, Nishimura G, Robertson SP, Savarirayan R, Sillence D, Simon M, Sutton VR, Warman ML, Superti-Furga A. Nosology of genetic skeletal disorders: 2023 revision. Am J Med Genet A. 2023;191:1164-209. PubMed PMID: 36779427.

Van Hul W, Boudin E, Vanhoenacker FM, Mortier G. Camurati-Engelmann Disease. Calcif Tissue Int. 2019;104:554-60 PubMed PMID: 30721323.

Verbruggen LA, Bossuyt A, Schreuer R, Somers G. Clinical and scintigraphic evaluation of corticosteroid treatment in a case of progressive diaphyseal dysplasia. J Rheumatol. 1985;12:809-13. PubMed PMID: 4057207.

Wallace SE, Lachman RS, Mekikian PB, Bui KK, Wilcox WR. Marked phenotypic variability in progressive diaphyseal dysplasia (Camurati-Engelmann disease): report of a four-generation pedigree, identification of a mutation in TGFB1, and review. Am J Med Genet. 2004;129A:235-47. PubMed PMID: 15326622.

Walton KL, Makanji Y, Chen J, Wilce MC, Chan KL, Robertson DM, Harrison CA. Two distinct regions of latency-associated peptide coordinate stability of the latent transforming growth factor-β1 complex. J Biol Chem. 2010;285:17029-37. PubMed PMID: 20308061.

Wong T, Herschman Y, Patel NV, Patel T, Hanft S. Repeat intracranial expansion after skull regrowth in hyperostotic disease: technical note. World Neurosurg. 2017;102:555-60. PubMed PMID: 28137547.

Yanagihara W, Wada T, Nomura JI, Saura H, Kubo Y, Ogasawara K. Camurati-Engelmann disease combined with transethmoidal meningoencephalocele: illustrative case. J Neurosurg Case Lessons. 2022;3:CASE21587. PubMed PMID: 36130541.

Yonezawa H, Hayashi K, Yamamoto N, Takeuchi A, Tada K, Miwa S, Igarashi K, Kimura H, Aoki Y, Morinaga S, Araki Y, Asano Y, Sakurakichi K, Ikeda H, Nojima T, Tsuchiya H. Significant improvement after surgery for a symptomatic osteoblastoma in a patient with Camurati-Engelmann disease: case report and literature review. Calcif Tissue Int. 2021;108:819-24. PubMed PMID: 33555353.

Yuldashev AJ, Shin CH, Kim YS, Jang WY, Park MS, Chae JH, Yoo WJ, Choi IH, Kim OH, Cho TJ. Orthopedic manifestations of type I Camurati-Engelmann disease. Clin Orthop Surg. 2017;9:109-15. PubMed PMID: 28261436.

License