

Case Report Article**Hearing loss in Camurati Engelmann disease: a case report****Anastasia K. Klagkou¹, Stavroula Koutroumpi², Constantinos Georganas³, Dimitrios Ioakimides¹,
Evaggelos Boulios¹, Georgia Tseliou¹***¹Department of rheumatology, General Hospital of Athens "G. Gennimatas, Greece; ²Department of endocrinology, Evaggelismos Hospital, Athens, Greece; ³Department of rheumatology, 251 General Airforce Hospital, Athens, Greece***Abstract**

Camurati-Engelmann disease (CED) is a rare autosomal dominant disease characterized by heavily thickened long bones, pelvis and skull. Deafness is a common finding, due to the compression of nerves and blood vessels by thickened skull bones, and is usually difficult to manage. Herein, we report a young female diagnosed with CED since her adolescence, with gradual deterioration of hearing of mixed type, where conservative medical treatment proved ineffective, confirming the key role of early decompressive surgery in such cases.

Keywords: Camurati Engelmann disease, Progressive diaphyseal dysplasia, Skull thickening, Hearing loss, TGF/β mutation

Introduction

Camurati-Engelmann disease (CED), also known as progressive diaphyseal dysplasia (PDD), or osteopathia hyperostotica scleroticans, is a rare genetic disorder. The gene responsible for CED has been identified on chromosome 19q13. It encodes the latency-associated peptide of transforming growth factor-β1 (TGF-β1), an important mediator of bone remodeling^{1,2}. The majority (7/10) of the mutations detected in CED are missense mutations located in exon 4, coding for the region in the latency associated peptide surrounding the residues responsible for homodimerisation (Cys223 and Cys225). Mutations of this gene result in increased transforming growth factor activity and subsequent stimulation of osteoblastic bone formation. Also, although these mutations were originally thought to result in suppression of the osteoclastic bone resorption, newer evidence suggests that they may actually promote the formation and activity of osteoclasts^{3,4}.

CED is characterized by progressive expansion and sclerosis, especially along the shafts of the long bones, and typically presents in childhood with generalized muscle weakness, lower limb pain, as well as a waddling gait⁵. Among common findings due to skull base thickening appears that of hearing loss, which may be conductive, sensorineural or mixed, and usually necessitates decompressive surgery.

This article reports the case of a patient diagnosed with CED, the significance of early diagnosis and treatment for the prevention of hearing loss.

Case Report

A 43-year-old female presented with an at least one year history of intermittent mild headache, and progressively deteriorating hearing loss. At the age of 15, she was diagnosed with CED disease, based initially on symptoms and typical radiological findings, which was further confirmed by genetic testing.

She complained of bone pain in all limbs, intense myalgia, generalized weakness, and progressive stiffness. On examination, extremities were long and slender, and severe scoliosis and frontal bossing were noted. She also had generalized hypertonia, hyperreflexia, and muscle wasting, leading to walking disability.

In order to evaluate the patient's reported symptoms we performed a complete laboratory set of exams which were unremarkable, except for increased bone turnover markers (Table 1). Radiographs of the long bones, vertebral column, and skull revealed symmetrical fusiform enlargement of the

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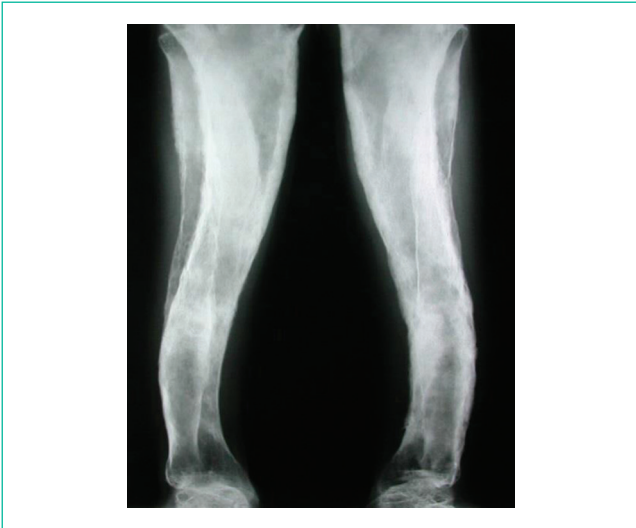


Figure 1. Symmetrical fusiform enlargement of the diaphyses of long bones.

	Result	Normal range
Serum calcium	9.1	8.2-10.2 mg/dl
Serum phosphorus	3.5	2.7-4.5 mg/dl
Bone Alkaline Phosphatase	127.5	11.6-30.6 U/L
Osteocalcin	196.6	12-41 ng/mL
2h urine Pyrilinks-D/Creatinine	90.2	3-7.4 nmol/ μ mol
2h urine Cross-Laps/Creatinine	595	80-420 μ g/ μ mol
Alkaline Phosphatase	353	40-104 U/L
Serum Creatinine	0.4	0.4-1.1 mg/dl
NTX urine/Cr urine 2h	111.3	20-50 BCE/mmol

Table 1. Patient's laboratory set of exams. *NTX: N terminal telopeptide, Cr: creatinine.*

diaphyses (endosteal and subperiosteal cortical thickening), thoracic and lumbar scoliosis, and osteosclerosis of the skull base respectively (Figures 1-3) Bone scintigraphy (Tc99MDP) showed diffusely increased skeletal tracer uptake, with a symmetrical distribution (Figure 4).

The skull was further studied with Computed Tomography (CT), which revealed diffuse hyperplasia and thickening of the skull bones, bilateral overgrowth of the internal auditory canals with compression of the vestibulocochlear nerves, and mild protrusion of the eye bulbs. Similar findings were present on Magnetic Resonance Imaging (MRI), which revealed no brain lesions. Ophthalmological clinical examination did not confirm any defect on visual acuity, pupil responses, color perception, or visual fields. Ear, throat, and nose (ENT) examination, and pure tone audiometry revealed

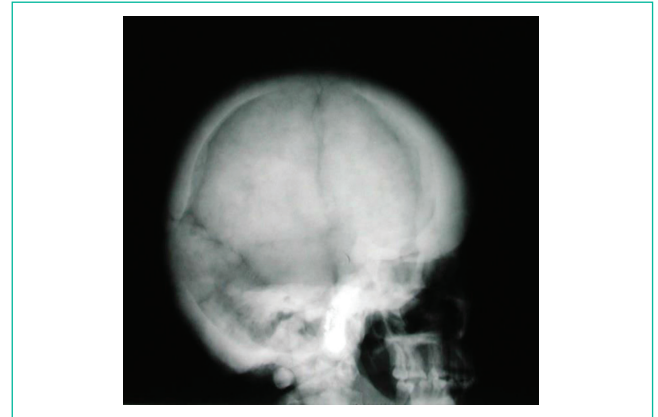


Figure 2. Osteosclerosis of the skull base and thickened calvaria.

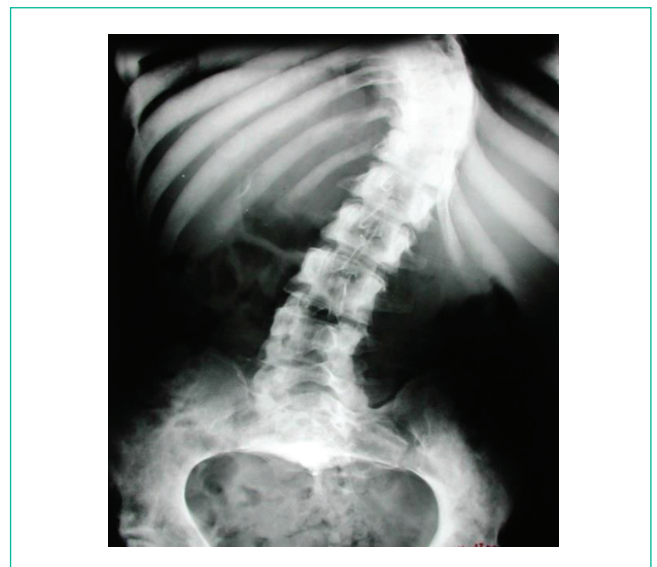


Figure 3. Thoracic and lumbar scoliosis.

both conductive and sensorineural hearing loss.

In order to treat the patient for the mixed hearing loss, we suggested surgical decompression. As the patient did not consent, a combined treatment with zoledronic acid (5 mg iv, single dose) and prednisolone 10 mg/day was offered. Patient's consent was obtained, since zoledronic acid is an off label therapy for CED. A conventional hearing aid was also used for hearing loss. Unfortunately, the patient did not demonstrate any hearing improvement, as confirmed by further ENT examination 6 months later.

Discussion

CED was first reported by Camurati in 1922, and further delineated by Engelmann in 1929^{6,7}. Neuhauser et al, in

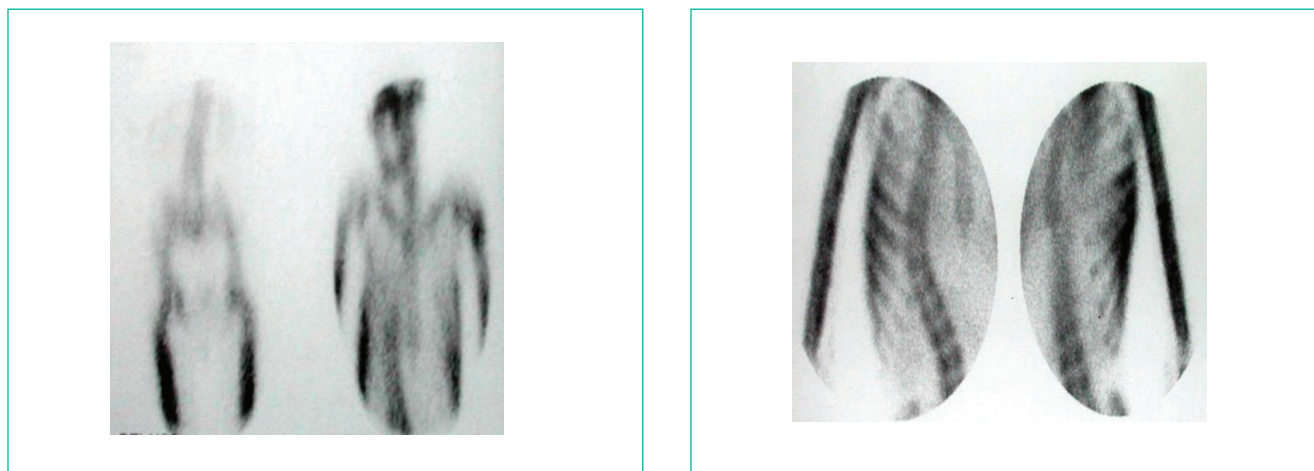


Figure 4. Increased tracer uptake in whole body scintigraphy (Tc99MDP) with symmetrical distribution.

1948, coined the term progressive diaphyseal dysplasia, stressing the diaphyseal location and the progressive features of the disorder⁸. It is characterized by progressive expansion and sclerosis, affecting mainly the diaphyses of the long bones. Pelvic bones, skull, mandible, and vertebrae are also thickened⁹⁻¹⁵. CED typically presents in childhood with generalized muscle weakness, lower limb pain, and a waddling gait⁵. Exophthalmos, and/or headache due to raised intracranial pressure by thickened skull bones, may be initial symptoms. Visual symptoms can occur, due to compressive optic neuropathy⁹. Diagnosis is initially based on the clinical picture, along with typical radiographic changes of the involved bones, while genetic testing is needed for the final diagnosis. Biochemical parameters are usually normal^{16,17}. In accordance with other reports, in our case, diagnosis was made since her adolescence based on typical signs and symptoms, confirmed further by radiological findings and at last by gene analysis. In particular, the last twelve months, headache and hearing deterioration were the main complaints. Comparison of previous with recent radiological imaging showed disease progression, especially a more intense thickening of skull bones, which could explain the worsening of neurological symptoms.

Given the rarity of CED, there are currently no randomized controlled trials documenting pharmacologic effectiveness of corticosteroid or bisphosphonate therapy. Multiple isolated reports document improvement in lower extremity gait coordination, muscle pain, exercise tolerance, and appetite after corticosteroid administration¹⁸⁻²². Bisphosphonate therapy has been met with less success; few reports document improvement, whereas most report no change^{20,23}. As documented from our patient's medical records, corticosteroids were offered for brief periods of time since her diagnosis, with good response on leg coordination, muscle pain, and appetite, until she presented to our department with progressively deteriorating hearing loss.

Hearing loss may be conductive, sensorineural or mixed.

Conductive hearing loss is caused by external auditory canal stenosis, secondary to eustachian tube narrowing, or overgrowth of the round window¹¹. Conductive hearing loss may be managed with conventional hearing aids, bone-anchored hearing devices, stapedectomy, or ventilation tube insertion^{10,24-27}.

In sensorineural hearing loss the root cause lies in the inner ear, or sensory organ (cochlea and associated structures), or the vestibulocochlear nerve (cranial nerve VIII), which are compressed, while mixed hearing loss is a combination of the above^{24,28-32}. There are several acquired conditions of the petrous temporal bone that may result in progressive internal auditory canal (IAC) stenosis, and these need to be considered in the differential diagnosis of Camurati-Engelmann disease. The most important pathologies include systemic disorders, such as Paget's disease of bone, cranial hyperostosis (van Buchem's disease), osteopetrosis (Albers-Schonberg disease), familial hyperphosphataemia, fibrous dysplasia, otosclerosis, and local conditions, such as osteomas, or exostoses of the IAC³⁰. In our case, since the diagnosis of CED had been already made, our work up was focused on distinguishing whether the site of the lesion was within the middle ear, the otic capsule, or the IAC, a combination of these, or involvement of all these sites. Also, a head-neck MRI was performed to exclude possible concomitant lesions. ENT examination revealed both conductive and sensorineural hearing loss after pure tone audiometry. In cases where progressive bony compression of the auditory nerve in the IAC is considered the only site of pathology causing a neural defect, decompressive surgery may be indicated^{24,28-34}.

Patients with severe sensorineural hearing loss are candidates for middle fossa or retrosigmoid IAC decompression^{10,28,35}. Staged cochlear implantation after adequate IAC decompression is beneficial for hearing

deterioration, even in case of critical IAC stenosis¹⁰. Fourteen total IAC decompressions in 11 patients, performed for hearing loss, vestibular symptoms, or facial nerve weakness were identified in literature, 8 of which demonstrated lasting hearing improvement, or stabilisation²⁴⁻³⁴. Two reports discuss isolated 15- and 8-Db high frequency sensorineural hearing loss (SNHL) after successful IAC decompression for vestibular symptoms; they implicate acoustic trauma or heat injury associated with prolonged drilling with a diamond burr^{28,29}. In our patient, decompressive surgery was not performed, due to patient's preferences, the medical treatment being the only option. Similarly to our case, other studies have shown no substantial benefit of any kind of hearing loss with conservative therapy.

Conclusion

Patients affected by CED necessitate a thorough work-up with Computed Tomography and/or Magnetic Resonance Imaging of the head and neck, especially in case of cranial involvement, since many of them could be asymptomatic. Annual ophthalmologic, ENT, and neurological examination should be considered. Hearing loss, especially in progressive disease, could be prevented if detected earlier, since earlier decompression may have better outcomes.

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