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Review Article

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The Role of Mutations on Gene TGFB1 in Camurati Engelmann Syndrome

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Abstract

Camurati-Engelmann disease (CED) is characterized by increased bone density primarily affecting the long bones of the arms and legs and the skull. The thickening of these bones leads to pain, a waddling gait, muscle weakness, and extreme fatigue. Increased density of the skull can cause a variety of neurological deficits such as headaches, hearing loss, vision problems, dizziness (vertigo), ringing in the ears (tinnitus), and even facial paralysis. The first symptoms of the condition can appear at varying ages, but usually during childhood, with pain and proximal muscle weakness developing by adolescence. CED is often diagnosed based on a physical exam and radiographic findings (X-rays). CED is inherited in an autosomal dominant manner and is caused by changes (mutations) in the TGFB1 gene.

Keywords: Camurati-Engelmann Syndrome, TGFB1 Gene, Long Bones, Hyperostosis.

Generalities of Camurati-Engelmann Syndrome

Camurati-Engelmann syndrome is a genetic disorder characterized by thick bones (hyperostosis) in the arms, legs, and skull. Thick bones in the limbs can lead to bone pain and muscle weakness in the arms and legs, and can quickly tire people with camurati-engelmann syndrome. Bone pain can range from mild to severe and can increase with stress, activity, or cold weather. Weak legs can also prevent you from standing, and some people with this syndrome experience gait instability. Additional limb disorders such as abnormalities in the knee joint, flat feet, swelling and redness in the limbs, and abnormal curvature of the spine may also occur in patients with camurati-engelmann syndrome [1].

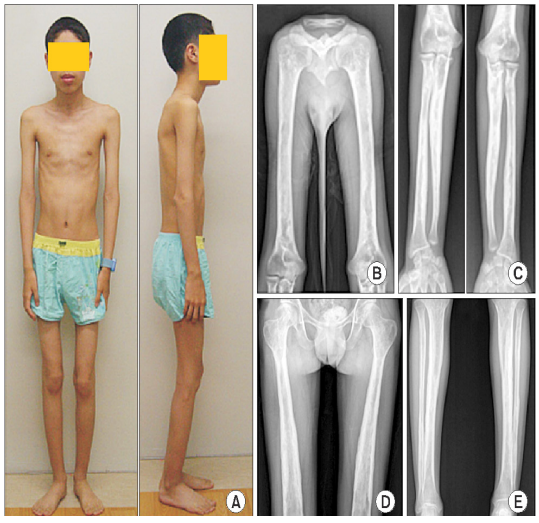

Figure 1: Images of a human with Camurati-Engelmann syndrome with skeletal disorders.

Clinical Signs and Symptoms of Camurati-Engelmann Syndrome
People with camurati-engelmann syndrome may have abnormal, thick skulls that can lead to abnormally large heads (macrocephaly), large mandibles, prominent foreheads, and drooping eyes (ocular proptosis). These changes in the head and face become more pronounced and spread with age. About a quarter of people with camurati-engelmann syndrome have a thick skull that increases brain pressure or compresses the spine, which can lead to a variety of neurological problems including headache, hearing loss, vision, dizziness, and tinnitus. And facial paralysis [1,2].

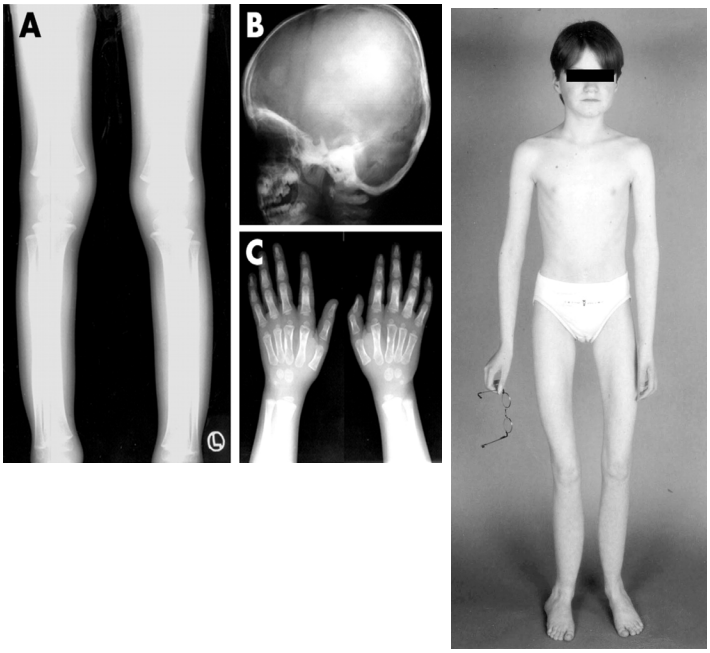

Figure 2: Another view of a boy with Camurati-Engelmann syndrome with skeletal disorder.

Other rare features of camurati-engelmann syndrome include abnormal longitudinal limbs relative to height, decreased muscle mass and body fat, tooth loss and decay, recurrent tooth decay, delayed puberty, and shortage of red blood cells (anemia). Enlarged liver and spleen (hepatosplenomegaly), thin skin, and excessive sweating of the palms of the hands, soles of the feet, and underarms (hyperhidrosis) [1,3].

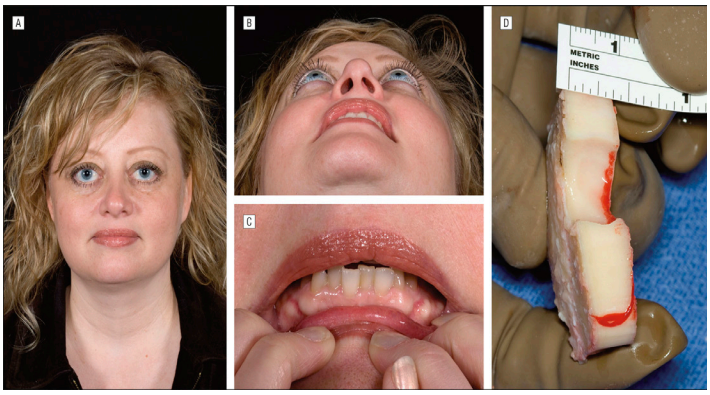

Figure 3: Images of a woman with Camurati-Engelmann syndrome with distinctive facial features.

Etiology of Camurati-Engelmann Syndrome

Camurati-Engelmann syndrome is caused by a mutation in the TGFB1 gene, which is located in the long arm of chromosome 19 as 19q13.2. This gene provides the instructions for the synthesis of a protein called growth factor-beta 1 (TGFβ-1). The TGFβ-1 protein produces biochemical signals that are responsible for various cellular activities such as cell growth and proliferation, cell maturation (differentiation), cell motility, and physiological cell death (apoptosis)[1,4].

The TGFβ-1 protein is found throughout the body but is particularly abundant in the tissues that make up the skeleton. This protein helps regulate the formation of bones and cartilage, the strength and flexibility of the tissues that make up most of the skeleton during early development. In addition, the TGFβ-1 protein is involved in various processes in other tissues [1,4].

Mutations in the TGFB1 gene, which causes camurati-engelmann syndrome, excessively increase the production and activity of the TGFβ-1 protein. This abnormal activity of the TGFβ-1 protein increases signaling, which leads to more bone formation. As a result, the bones in the arms, legs, and skull will be thicker than normal, causing movement and neurological problems in people with camurati-engelmann syndrome [1,4].

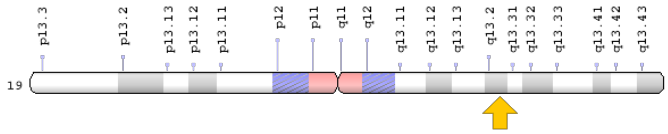

Figure 4: Schematic of chromosome 19 where the TGFB1 gene is located in the long arm of this chromosome as 19q13.2.

Camurati-Engelmann syndrome follows an autosomal dominant inheritance pattern. Therefore, a copy of the TGFB1 mutant gene (either parent) is required to cause the syndrome, and the chance of having a child with the autosomal dominant syndrome is 50% for each possible pregnancy [1,6].

Frequency of Camurati-Engelmann Syndrome

camurati-engelmann syndrome is a rare genetic disorder whose prevalence is unknown worldwide. So far, more than 300 cases of this syndrome have been reported in the medical literature from around the world [1,5].

Diagnosis of Camurati-Engelmann Syndrome

Camurati-Engelmann syndrome is diagnosed based on clinical and physical findings of patients and some pathological tests. The most accurate way to diagnose this syndrome is to have a molecular genetic test for the TGFB1 gene to check for possible mutations. Prenatal diagnosis is also possible using the PGD technique and amniocentesis fluid or biopsy of the chorionic villi of the fetal placenta [1,6].

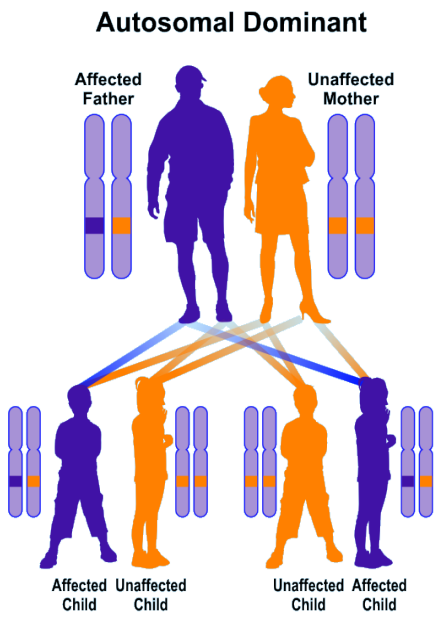

Figure 5: Schematic of the autosomal dominant inheritance pattern followed by Camurati-Engelmann syndrome.

Treatment options for Camurati-Engelmann Syndrome

The treatment and management strategy of camurati-engelmann syndrome is symptomatic and supportive. Treatment may be coordinated by a team of specialists including an orthopedist, a neurologist, a hematologist, a nutritionist, a liver and spleen specialist, a dermatologist, surgeons, and other health care professionals. There is no definitive treatment for this syndrome and all clinical measures are taken to alleviate the suffering of the patients. Genetic counseling also has a special place for all parents who want a healthy child [1,6].

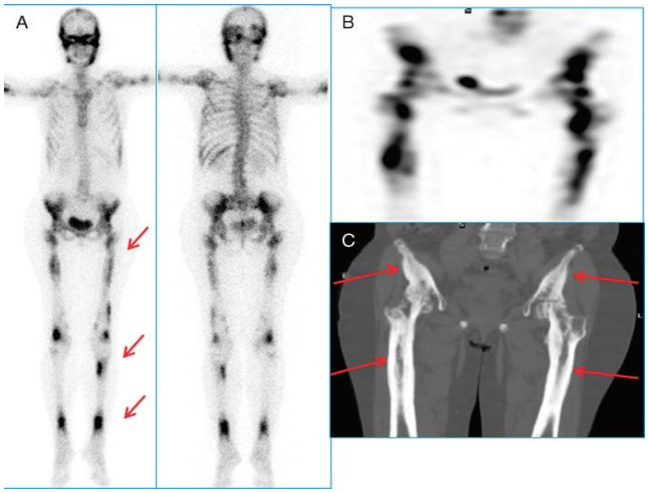

Figure 6: Radiological images of disorders related to Camurati-Engelmann syndrome1.

History of Camurati-Engelmann Syndrome.

Camurati-Engelmannn syndrome was first reported in 1987 by M. Camurati and G.Engelmann [1,6].

Discussion and Conclusion

The signs and symptoms of CED can be extremely variable even among affected family members. Some individuals with a TGFB1 mutation do not develop signs or symptoms of the disease or evidence of increased bone density on X-ray examination (i.e., reduced penetrance). CED is caused by mutations in TGFB1 which encodes transforming growth factor beta-1 protein. This protein helps control the growth and proliferation of cells, the process by which the cells mature and begin to specify (differentiate), cell movement, and cell directed self-destruction (apoptosis). Treatment for CED consists of management of symptoms. To manage the pain caused by the thickening of the bones, individuals may be treated with corticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs). For those with hearing problems caused by the thickening of the bones of the base of the skull, decompression surgery in which a small piece of the base of the skull is removed has been done in some individuals with mixed results. This procedure can result in an increased risk of complications as well as the possibility for bone to re-grow after the surgery [1-6].

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