Skeletal Dysplasia Presenting as a Neuromuscular Disorder – Report of a Family with Camurati-Engelmann Syndrome

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ABSTRACT

We report the case of a 28-year-old female with progressive diaphyseal dysplasia, who presented with history of a similar neuromuscular condition. Clinical, radiological and molecular data confirmed Camurati-Engelmann Disease (CED). This is the first Romanian family who was diagnosed with CED.

Keywords: Camurati-Engelmann disease, skeletal dysplasia, TGFB1 gene mutation

BACKGROUND

Camurati-Engelmann Disease (CED) (MIM 131300), also known as Progressive diaphyseal dysplasia, is a rare autosomal dominant bone dysplasia condition. It was first described by Camurati in 1922 (1) and then by Engelmann in 1929 (2). Radiologically, the typical feature of this disorder is represented by hyperostosis of the long bones, which is bilateral and symmetrical. TGFB1 is the only gene known to be associated with CED (3).

MATERIAL AND METHODS

The patient, a female of 28 years old, was self-referred to Genetics Department for a condition imitating primary myopathy: muscular weakness, waddling gait, pain in the extremities, enlarged lower limbs, but with decreased subcutaneous fat, easy fatigability, pulmonary symptoms (coughing, frequent respiratory distress), associated in time with hearing loss, headache, vision changes (blurred vision, intermittent diplopia), vertigo, hyposmia, facial paralysis. She has these symptoms of this disorder since childhood, when she was 4-years-old and all these features grew until her late 20s. She was initially diagnosed with congenital myopathy due to a long-standing history of muscle weakness. Because of this clinical report, paired with limitation of joint movements, we recommended skeletal survey, which revealed as principal radiographic finding the hyperostosis of major long bones diaphyses due to proliferation of osseous tissue on
perioisteal and endosteal surfaces. Osteosclerosis involved also the skull (Figure 1). Diagnosis of Camurati-Engelmann Disease (CED) was then considered. Additional examinations, such as neurological and ophtalmological evaluations confirmed the intermittent appearance of abnormal clinical features of the patient, being deeply influenced by chronic anti-inflammatory treatment. Also, ENT (ear-nose-throat) report confirmed symptomatology of the patient from last period. Other investigations, such as computed tomography of the skull were not performed. Family history revealed other family members with the same condition. Her brother of age 25 and the father were discovered with similar clinical and radiographic skeletal findings, but the phenotype of the father was generally less severe. From clinical point of view he presented with a mild form of muscular picture, accentuated during exercises, without other abnormal features: no extremity pain, without neurological symptoms. The radiological images confirmed the presence of skull base sclerosis and abnormal skeletal survey of the long bones, but in an easier form (Figure 2). The family pedigree demonstrates the autosomal dominant inheritance pattern (Figure 3).

Molecular genetic testing was performed for the proband, her brother and her daughter. We analysed exon 4 of the TGFBI gene by PCR and bi-directional sequencing.

For all members of the family a written consent to be studied was obtained.

RESULTS

Genetic analysis of the TGFBI gene revealed a heterozygous missense mutation c.668G>A or p.Cys223Tyr in exon 4 of the TGFBI gene for the female and her brother. The mutation results in the exchange of the conserved amino acid cystein 223 for a tyrosine and is predicted to be disease causing, confirming the clinical diagnosis of Camurati-Engelmann syndrome. Also, the analysis for her daughter was performed and it was negative. This is the first Romanian family who was diagnosed with CED.

FIGURE 1. Radiographic examination of the patient: A. sclerosis of the skull base; B. enlarged and sclerotic dyaphises – antero-posterior view of the knees; C. proliferation of osseous tissue on periosteal and endosteal surfaces – lateral view of the knee.

FIGURE 2. Radiographic skeletal findings of the family: A. patient’ brother: cortical thickening, narrowing of medullary cavity B. skull base involvement of patient’ father; C. Knee joints of the father with hyperostosis of the long bones.
DISCUSSION

Camurati-Engelmann disease is caused by mutations of the transforming growth factor beta 1 (TGF beta1) gene on chromosome 19q13.1-q13.3 (4) (5), which comprises seven exons. TGFβ1 (transforming growth factor-beta-1) is a member of the TGFβ1 signaling pathway and regulates cell proliferation, migration, differentiation and apoptosis. TGFβ1 is particularly abundant in the bone matrix, where it is involved in the regulation of bone formation and resorption. Mutations in different domains of the TGFβ1 gene lead to inherited sclerosing bone disorder or osteoporosis (6).

The majority of mutations are missense mutations in exon 4 leading to single amino acid substitutions in the encoded protein (7). Three pathologic variants in exon 4 of the TGFβ1 gene account for approximately 80% of the mutations observed in CED (8). There may be CED variants without defects in TGFβ1. A second form of CED (CED type II) featuring stria tions of the bones was proposed (9).

The onset of the disease is usually during childhood and in most of the cases before the age of 30. Our proband presented with suggestive phenotype since her childhood, around the age of 4 years, with pain of the lower limbs, and later, after age of 16 years with muscle weakness and wide-based, waddling gait and respiratory problems. Her brother has a similar history.

Bone pain is described in 90% of affected individuals, more intense in the lower limbs (8). Also, bone tenderness, intermittent limb swelling were reported (10). Most clinical features are secondary to the hyperostosis and sclerosis of the skeleton. The tibia is the most commonly affected bone, followed by the femur, fibula, humerus, ulna, and radius. The metaphysis and epiphysis are typically not involved, since these regions are formed by enchondral ossification (11).

Facial features such as frontal bossing, enlargement of the mandible, proptosis and cranial nerve impairment resulting in facial palsy are seen in severe cases later in life. Neurologic symptoms are related to the affection of the cranial base, with bony overgrowth of the skull base, with possible foraminal stenosis and diminished cranial vault volume and increased intracranial pressure. Although more than 50% of patients with CED will have confirmed skull base involvement on radiologic assessment, less than 25% experience cranial nerve dysfunction (10,12).

In our study the proband complained of hearing loss, headache, hyposmia, vision changes and facial paralysis as manifestations of cranial base involvement.

Occasionally, systemic manifestations can occur: hepatosplenomegaly, anemia, leucopenia (8), but they were not found to our patient.

There is no correlation between the nature of TGFβ1 mutations and the severity of the clinical manifestations of CED, there is a marked intrafamilial clinical variability and supporting incomplete penetrance of CED was observed (13). In some instances, the disease may regress by adulthood (14). Also, additional genetic factors involving in modulation the outcome of the principal mutation were discussed (8). The extreme phenotypic variability of this disorder can cause difficulties in genetic counseling. In our study the proband and her brother were the most severely affected individuals of the family, but the phenotype of the father was mild.

Management of the patients with CED is very difficult and complex, depending on clinical picture and their evolution.

Therapy with corticosteroids should be attempted in all symptomatic patients (15). Several studies showed that steroids may be recommended as an effective method of treatment (16) because can delay bone hyperostosis and prevent or delay the onset of skull involvement and reduce pain and weakness, improving gait, exercise tolerance, and flexion contractures (15). Another study underlined that corticosteroids improve the quality of life but don’t alter the course of the disease (17). The medical therapy has not been successful in treating as-
associated skull base symptoms, surgery with bony decompression remaining the only way to treat the patients with advanced disease (12). Hearing evaluation includes serial examinations. The etiology of deafness associated with this rare condition is the narrowing of the internal auditory canals cause by bony encroachment on nerves and vessels (18). Losartan can be used in symptomatic individuals who do not tolerate corticosteroids, with clinical improvement of physical activities (19). A periodic complete neurologic exam should be done and monitoring of blood pressure must be a part of surveillance of the patient with CED because hypertension can develop secondary to steroid therapy (15).

Our family represents a good example of the complementary nature of the clinical, radiological and molecular findings to consider individual treatment options.

**CONCLUSION**

Diagnosis of this disorder is based on the clinical history, family details, physical examination and skeletal survey. Considerable variations in signs, symptoms and severity between affected individuals could exist, also within the same family.

Many patients who present symptoms of pain in lower limbs, muscle weakness, waddling gait are often incorrectly diagnosed with muscular dystrophy or delayed diagnosis.

Early recognition, genetic diagnosis and genetic counseling play a crucial role in the management of the patients with this disorder.

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**REFERENCES**


