Diagnostic, treatment and outcome possibilities in achondroplasia

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Abstract

Introduction. Achondroplasia is a common form of chondrodysplasia. It is transmitted by autosomal dominant trait. The disease is determined by mutations in receptor-3 gene of the fibroblast growth factor. The most frequent mutations are c.1138G>A and c.1183G>C; c.1138A. The diagnosis can usually be made on the basis of clinical characteristics and specific features on radiographs. It is not necessary to perform molecular testing in every child with a clinical diagnosis of achondroplasia.

The aim of this study is to establish the diagnostic, treatment and outcome possibilities in patients with achondroplasia in our care.

Method. The study group consisted of 27 patients with achondroplasia. The method consisted of: clinical and radiological examinations. The DNA analasys was performed by PCR-RFLP technique.

Results. 80 patients were diagnosed with bone dysplasia; 24 of them were diagnosed (on clinical and radiological basis) with achondroplasia. Out of this group, 16 patients were identified as heterozygotes for G1138A mutation in FGFR3 gene; 3 patients undergoing treatment with somatotropic hormone; the growth rate is improving from 0.1 cm/month to 0.5 cm/month.

Conclusions. In achondroplasia diagnosis is based on clinical and radiological criteria. It is the first study that reports the prevelance of this mutation in Romania.

Keywords: achondroplasia, chondrodysplasia, molecular diagnostic techniques, child, Romania

Introduction

Achondroplasia (OMIM 100800) is a common form of chondrodysplasia with a frequency of 1/25.000 – 1/30.000 newborns [1]. This, in turn, translates into 250,000 affected persons worldwide [2,3].

The achondroplasia phenotype has been recognized for thousands of years, as evidenced in the artifacts of many different cultures [4], and remains the most readily recognizable of the dwarfing disorders. The term seems to have been first used in the nineteenth century, and the main features were described shortly thereafter.

It is transmitted by an autosomal dominant inheritance pattern with full penetrance and shows only modest variability of expression. Because of its dominant inheritance pattern, an individual affected by achondroplasia (and whose partner is of average height) has a 50% risk for each of their offspring to be similarly affected. However, most instances of achondroplasia (approximately 75-80% of the cases) are caused by de novo mutations. In turn, around 80% of affected babies are born to two unaffected, average height parents [1].

The disease is determined by mutations in the fibroblast growth factor receptor-3 gene (FGFR3), mapped to band 4p16.3, resulting in decreased endochondral ossification, inhibited proliferation of chondrocytes in growth plate cartilage and decreased cartilage matrix. The most frequent mutations (up to 98%) are c.1138G>A and c.1138G>C; c.1138G>A, a transition mutation (Gly>Arg) at nucleotide 1138 in codon 380, in the transmembrane domain has

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been associated with more than 97% of the known cases of achondroplasia. Only 1% of patients with achondroplasia have a G to C point mutation at the same site (c.1138G>C) [5-7]. Mutation analysis of patients with achondroplasia showed that nearly all mutations arise on the paternal chromosome. The paternal origin of the mutation in FGFR3 correlates with advanced paternal age in the cases examined in literature [6]. There is no recognized ethnic or sex predisposition [8].

The diagnosis can usually be made on the basis of clinical characteristics and specific features on X ray. It is not necessary to perform molecular testing in every child with a clinical diagnosis of achondroplasia. However, FGFR3 testing should be considered when a confirmed achondroplasia diagnosis is needed [8].

The diagnosis of achondroplasia in the fetus is made most often with certainty when one or both biological parents have this condition. More often, the scenario presents when the diagnosis of achondroplasia is suspected late in gestation on the basis of long bone foreshortening incidentally discovered via ultrasonography in the fetus of an average-stature couple [8]. At 32 weeks, shortening of the proximal aspect of the limbs, increased biparietal diameter (over the 95th percentile) and a short nasal bridge are clinical findings associated with achondroplasia. Confirmation of diagnosis on the basis of ultrasonographic features characteristic of achondroplasia can be provided by molecular testing (FGFR3 mutational testing) of a prenatal specimen (chorionic villus sampling at 11 – 13 weeks gestation or amniocentesis after 15 weeks gestation) [8].

After birth: the average length for male newborns is 47.7 cm and 47.2 cm for female babies, additional findings of macrocephaly with frontal bossing, a hypoplastic middle third of the face, Trident hand, shortening of the hand and fingers, short limbs due to a shorter than average proximal segment, long and narrow thorax.

As a newborn and afterwards, as a baby, the motor development is stunted due to muscle hypotonia, with the psychomotor development being age-appropriate. The patients often present with dorso-lumbar kyphosis, which improves under kinesiotherapy, and hyperlaxity of the distal joints, with a limited extension of the elbow.

In the teenage years and as a young adult, patients present with severe short stature (final expected height for men is 125 cm, and for women 120 cm), with a shortened proximal limb segment and a relatively long thorax, with marked hyperlordosis.

The diagnosis can usually be made on the basis of clinical characteristics and specific features on radiographs, including a square shape of the pelvis with a small sacrosciatic notch, short pedicles of the vertebrae with interpedicular narrowing from the lower thoracic through lumbar region, rhizomelic (proximal) shortening of the long bones, proximal femoral radiolucency and a characteristic chevron shape of the distal femoral epiphyses [8].

The aim of this study is to elaborate on the diagnosis, treatment and outcome possibilities in patients with achondroplasia in our care.

Patients and method

The study group consisted of 27 patients (17 girls and 10 boys), aged between 1 year 8 months – 22 years, who were registered in the Centre of Genetic Diseases of First Pediatric Clinic Cluj between 2011-2019. The method consisted of: clinical assessment and radiological examinations (X rays of the skull, upper and lower limbs, spinal column and pelvis). The DNA analysis was performed by PCR-RFLP technique.

Results

Between 2011 - 2019, 80 patients were diagnosed with bone dysplasia in our clinic; 27 of them (33.75%) were diagnosed (on clinical and radiological basis) with achondroplasia. All these patients presented with disharmonic short stature, the specific craniofacial features and bone and joint anomalies of achondroplasia. Out of this group, 16 patients (59.25%) were identified as heterozygotes for the G1138A mutation in FGFR3 gene. In the 3 patients (18.75%) undergoing treatment with somatotropic hormone, the growth rate showed improvement from 0.1 cm/month to 0.5 cm/month.

Discussion

In our study only 16 patients (59.25%) were identified as heterozygotes for the G1138A mutation in the FGFR3 gene. Alderborn A et al investigated DNA from 16 Swedish patients with achondroplasia for the presence of this mutation. All patients were found to be heterozygous for the G to A transition at nucleotide 1138 [10]. 70 of 75 Japanese patients with achondroplasia were found to have G1138A mutation in FGFR3, and two patients had a G1138C mutation [11]. In another study (He X) out of 12 cases of achondroplasia, including 10 sporadic cases and 2 cases in a pedigree, 11 cases were identified as caring the c.1138G>A heterozygous mutation, and one case was identified as caring the c.1138G>C heterozygous mutation. Exon 8 of the FGFR3 gene was analyzed in 40 patients with achondroplasia and in all cases the c.1138G>A mutation was found [5].

The probable cause for the comparably low presence of this mutation in our study group likely lies in the criteria used for the clinical and imaging diagnosis. Mutations in FGFR3 may cause 2 other syndromes with similar clinical presentations to achondroplasia: namely, hypochondroplasia and thanatophoric dysplasia. Regarding hypochondroplasia, the same clinical features noted in achondroplasia may be present, but in a milder clinical form. By contrast, thanatophoric dysplasia presents with

severe thoracic and lung hypoplasia, which are expected to be lethal in the pre- or early post-natal period [8].

In our study, for the 3 patients (18.75%) undergoing treatment with somatotropic hormone; the growth rate showed improvement from 0.1 cm/month to 0.5 cm/month. An increase in growth velocity was reported following short term GH treatment, but no clear benefit was established for long term treatment. However, the effect on body proportion is still unknown and currently the use of GH to treat achondroplasia is not routinely reccomended [6].

Conclusions

The diagnosis of achondroplasia is chiefly based on clinical and radiological criteria. To our knowledge, this is the first study to report the prevalence of the above-mentioned mutations in a Romanian group of patients.

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