

Achondroplasia current concept of orthopaedic management

Gabriel T Mindler^{1,2,3} , Alexandra Stauffer^{1,2}, Catharina Chiari^{1,2}, Kiril Mladenov^{4,5}, and Joachim Horn^{1,4,7}

Abstract

Achondroplasia, the most common form of inherited disproportionate short stature, is caused by mutations in the fibroblast growth factor receptor 3 gene. The typical clinical features of achondroplasia include short stature, rhizomelic disproportion, joint hyperlaxity, spinal deformity and deformity of the upper and lower limbs. The latter are among the challenges of state-of-the-art orthopaedic treatment plans and significantly contribute to the burden of the disease in individuals with achondroplasia. Multidisciplinary preoperative individual decision-making concerning surgical interventions should be considered. New medical treatments for achondroplasia have been developed and (some) have been approved for clinical use in several countries. While the number of research articles on achondroplasia is increasing rapidly, many unknown or controversial orthopaedic topics remain. Furthermore, in view of new medical developments with improvements in growth and potentially other effects, the timing and algorithms of orthopaedic treatments (e.g. guided growth, limb lengthening and deformity correction) need to be re-evaluated. While standing height is the primary research focus in medical therapy, it is crucial to comprehensively assess orthopaedic parameters in this multifactorial disease. The current treatment of patients with achondroplasia requires specialised multidisciplinary centres with transitional care and individual orthopaedic counselling.

Keywords: Deformity, achondroplasia, multidisciplinary, rare disease, transition

Introduction

Genetics/pathophysiology

Achondroplasia is the most common form of inherited disproportionate short stature with full penetrance caused by an autosomal dominant gain-of-function mutation in fibroblast growth factor receptor 3 (FGFR3).¹ This germline missense mutation results in ligand-independent activation of FGFR3 and its signalling pathways, with subsequent inhibition of chondrocyte proliferation and differentiation.^{2,3} Other types of skeletal dysplasias are associated with missense mutations in FGFR3, ranging from mild, such as hypochondroplasia, to severe, such as severe achondroplasia with developmental delay, acanthosis nigricans syndrome or thanatophoric dysplasia, depending on localisation within the tyrosine kinase domain.¹

Longitudinal bone growth not only requires bone elongation by chondrocyte proliferation and hypertrophy but also elongation of the perichondrium and periosteum.⁴ In the endochondral bone, FGFR3 is expressed in the resting and

proliferating zones of the growth plate and negatively regulates the proliferation and differentiation of chondrocytes when activated.^{1,2} FGFR3 activation and its subsequent pathways lead to the inhibition of terminal hypertrophic differentiation of

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