International Journal of Paleopathology 3 (2013) 243–256

Contents lists available at ScienceDirect

International Journal of Paleopathology

journal homepage: www.elsevier.com/locate/ijpp

Research Article

# Osteological evidence of short-limbed dwarfism in a nineteenth century Dutch family: Achondroplasia or hypochondroplasia

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ARTICLE INFO

*Article history:*
Received 29 April 2013
Received in revised form 11 August 2013
Accepted 12 August 2013

*Keywords:*
Dwarfism
Skeletal dysplasia
Historic cemetery
Family history

ABSTRACT

An opportunity to explore osteological features of a form of disproportionate dwarfism is presented by a recent archaeological discovery. Excavation of a predominately nineteenth century Dutch cemetery from the rural, agricultural village of Middenbeemster revealed an older adult female with skeletal changes consistent with achondroplasia. The most marked features are a rhizomelic pattern of shortened and thickened upper and lower limbs, frontal bossing and a moderately depressed nasal bridge, small lumbar neural canals with short pedicles, bowing of the femora and tibiae, and short stature (130.0 ± 5 cm). However, some common features of achondroplasia like cranial base reduction and shortened fingers and toes are absent. The alternative diagnosis of a more mild form of short-limbed dwarfism, hypochondroplasia, is explored and aided by archival identification of the individual and her offspring. Five offspring, including three perinates, a 10-year-old daughter, and a 21-year-old son, are analysed for evidence of an inherited skeletal dysplasia. The unique addition of family history to the paleopathological diagnostic process supports a differential outcome of hypochondroplasia. This combination of osteological and archival data creates a unique opportunity to track the inheritance and manifestation of a rare disease in a past population.



## 1. Introduction

A recent discovery from the excavation of a predominately nineteenth century cemetery, Middenbeemster, in the Netherlands, provides the opportunity to investigate the features and inheritance of a form of disproportionate dwarfism: achondroplasia or hypochondroplasia. An older adult female (numbered V0945) presented with marked rhizomelic shortening of the limbs, with a reconstructed stature of 130.0 ± 5 cm, and several other cranial and postcranial abnormalities. Archival records identify her as a 66-year-old female named Sara R.[1] (AD 1797–1863), who married a carpenter named Brant O. Records indicate she gave birth to seven children, two of whom were stillborn, one who died at three-days of age, one who died at the age of 10-years, one who died at the age of 21-years, and two who lived into old adulthood. Fertility in achondroplastic females is usually normal (Allanson and Hall, 1986), although higher rates of infertility, dysmenorrhea and early menopause have been suggested (Ghumman et al., 2005). If the pelvis is misshaped or narrow vaginal delivery is difficult, causing increased morbidity and mortality risks for mother and child (e.g. Kozma et al., 2011). The five youngest offspring were buried in the Middenbeemster cemetery and are analysed. The unique opportunity to examine the known offspring of an individual with a skeletal dysplasia adds greatly to the diagnostic process.

The objectives of this study are to: (1) present the skeletal features of individuals with a purported form of disproportionate dwarfism in order to improve our knowledge of the range of phenotypic changes that may be encountered; (2) present the analysis of the affected individual's offspring in order to draw attention to the manifestation of disproportionate dwarfism in subadults (<18 years of age); and (3) engage in a differential diagnosis focussed on achondroplasia and the comparatively less well-known hypochondroplasia, in order to make the most accurate diagnosis.

### 1.1. Background: achondroplasia and hypochondroplasia

Disproportionate or short-limbed dwarfism accounts for over three quarters of the approximately 200 types of dwarfism, with achondroplasia by far the most common form. Achondroplasia prevalence estimates range from one in 10,000 to one in 40,000, with some agreement on a universal rate of one in 25,000 (Horton et al., 2007; Oostra et al., 1998; Stoll et al., 1989). Achondroplasia is relatively well-documented from skeletal remains in a range of past populations (Arcini and Frölund, 1996; Farkas et al., 2001; Frayer et al., 1988; Gładykowska-Rzeczycka, 1980; Knol et al., 1996;

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[1] Full last names are omitted because of ethical considerations.

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http://dx.doi.org/10.1016/j.ijpp.2013.08.004

Kozma, 2006; Kozma et al., 2011; Larje, 1985; Polet and Orban, 1996; Sables, 2010; Slon et al., 2011; Snow, 1943), as well as from material culture depictions (Bernal and Briceno, 2006; Enderle, 1998; Haworth and Chudley, 2001; Rodriguez et al., 2012). Over 99% of achondroplasia cases are caused by mutations of the fibroblast growth factor receptor-3 (*FGFR3*) gene on chromosome 4 (Rousseau et al., 1994; Shiang et al., 1994). In normal individuals *FGFR3* functions as an inhibitor to the proliferation and terminal differentiation of growth plate chondrocytes (Deng et al., 1996). In achondroplasia the mutated receptor is constitutively active and exaggerates the normal physiological process (Horton et al., 2007) leading to slow cartilage-to-bone turnover so that bones that grow by endochondral ossification (e.g. the limb bones) become shortened (Horton et al., 2007). By adulthood, height ranges from 118 to 145 cm for males and 112 to 136 cm for females (Horton et al., 1978; also see Hunter et al., 1996). Bones that grow via intramembranous ossification (e.g. the cranial vault), or endochondral bones with a slow growth rate, are less affected, explaining why this type of dwarfism is classified as disproportionate.

Clinical research has found that 80–90% of achondroplasia cases are de novo, while 10–20% of cases are a result of the mutation being passed down from an affected parent (Vajo et al., 2000). Achondroplasia has an equal chance of occurring in either sex and because the mutated allele is dominant, an affected parent has a 50% chance of passing it on. The mutation has complete penetrance, meaning that all individuals will have clinical symptoms. However, there is variation in the severity of phenotypic change (in part due to the extent of changed *FGFR3* signalling) such that major and mild forms of achondroplasia are recognised (Rimoin, 1988).

In addition to achondroplasia, a milder form of short-limbed dwarfism, hypochondroplasia, also results from mutation to the *FGFR3* receptor (Bellus et al., 1995, 1996). The milder clinical and radiographic features of hypochondroplasia include short arms and legs, with less overall height reduction, on the order of two to three standard deviations below the population mean (male stature range of 138–165 cm; female stature range of 128–152 cm) (Appan et al., 1990; Maroteaux and Falzon, 1988; Oberklaid et al., 1979; Walker et al., 1971). As in achondroplasia, the cranium is normal to large in size (macrocephaly), often appearing especially large in comparison to the underdeveloped appendicular skeleton (Oberklaid et al., 1979; Walker et al., 1971). Hypochondroplasia is often differentiated from achondroplasia by the lack of changes to the facial skeleton (Francomano, 2005; Langer et al., 1967; Wynne-Davies et al., 1981; although see Oberklaid et al., 1979). An important clinical marker of achondroplasia and hypochondroplasia is the failure of caudal increase in the interpedicular distance of lumbar vertebrae 1–5 because of early fusion of the pedicles to the vertebral bodies at the neurocentral synchondrosis (Appan et al., 1990; Jeong et al., 2006; Srikumaran et al., 2007). Finally, the following features that are common in achondroplasia may occur in hypochondroplasia, but are less likely to be severe or even to form at all: long bone thickening, lower limb bowing, lumbar lordosis, and short and broad hands, feet, and os coxae (Oberklaid et al., 1979; Walker et al., 1971). Because the features of hypochondroplasia are less pronounced, it is usually diagnosed at a later age, and can even go undiagnosed as taller hypochondroplastics merge with the shorter members of the general population (Francomano, 2005; Oberklaid et al., 1979). Hypochondroplastics have a thick, muscular appearance often described as 'stocky' (Francomano, 2005).

The prevalence of hypochondroplasia is not well known for several reasons: its more recent recognition as a distinct clinical entity; the lack of agreement for a set of diagnostic criteria; the overlap in phenotype between achondroplasia on the one end and 'normal or unaffected' on the other end, and that no single morphological or radiological feature is unique to hypochondroplasia (Almeida et al., 2009; Oberklaid et al., 1979). Some clinicians have discussed the two diseases as a single complex (the hypochondroplasia–achondroplasia complex) (Sommer et al., 1987). They do, however, result from different *FGFR3* mutations and since the late 1990s are easily distinguished with genetic testing. Francomano (2005) notes that general agreement is emerging that the prevalence of hypochondroplasia is similar to that of achondroplasia. Given this, it would be expected that hypochondroplasia occurred at a similar rate as achondroplasia in past populations. Yet, to our knowledge hypochondroplasia has never been documented in a paleopathology context, in contrast to the comparatively well-documented achondroplasia. It is important to recognise hypochondroplasia in past populations to get an accurate understanding of congenital conditions. Moreover, in osteoarchaeology short stature is often attributed to nutritional stress, but other causes, such as hypochondroplasia, should be taken into consideration.


**Fig. 1.** Middenbeemster, The Netherlands.

## 2. Materials

The Middenbeemster cemetery (Fig. 1) was in use from AD 1612 to 1866. According to archival documents most skeletons date to the nineteenth century. Approximately 450 individuals were excavated by Leiden University and the archaeology company Hollandia Archeologen in 2011. Individual V0945 was interred in a normal-sized coffin, and skeletal preservation and completeness are very good. All of the offspring have preservation and completeness that are good to very good.

Middenbeemster was located in the centre of the Beemster municipality, a rural community of mainly dairy farmers and labourers. There are various archival documents for the Middenbeemster community spanning the seventeenth to nineteenth century. Amongst these is a cemetery ledger that contains the name, age-at-death, parents, marriage, and occupation for most of the individuals interred between AD 1829 and 1866. From the post-Mediaeval period there are also military archives assessing fitness for most males over the age of 18 years, listing height and major diseases/anomalies. Table 1 shows the osteological and archival information for each of the analysed individuals. We have some archival information about individual V0945's parents but not their skeletons.

### 2.1. Methods

Osteological examination was conducted prior to acquiring archival information about age, sex and stature. For the adults,