INNSPUB

International Journal of Biosciences | IJB |
ISSN: 2220-6655 (Print), 2222-5234 (Online)
http://www.innspub.net
Vol. 16, No. 3, p. 371-375, 2020

RESEARCH PAPER OPEN ACCESS

Skeletal dysplasia: a series of five cases of Bangladesh demonstrating classical achondroplasia

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Key words: Achondroplasia, RAMP disorder, Cataract, Foot abnormality.

http://dx.doi.org/10.12692/ijb/16.3.371-375 Article published on March 29, 2020

Abstract

Achondroplasia is a metaphyseal dysplasia, mediated by *FGFR3* gene mutation that results in abnormalities in cartilaginous bone growth which manifests in short limbs and rhizomelic disproportion of varying degrees of severity. Sufferers, such as those that have been presented here, complain of unabated limited range of motion and various other associated medical symptoms. The disorder is inherited as autosomal dominant and *de novo* mutations arise rather frequently in the general population. This text explores five similar and undiagnosed cases, whose external phenotype and associated medical symptoms are evidence of the classical achondroplasia, with description of a few unusual reported symptoms such as genetic bilateral cataract, and foot deformity. The alarming frequency of cases warrants greater attention by medical practitioners and researchers, and general awareness.

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Introduction

Achondroplasia is one of themany causes of dwarfism, and the most common (80%) which is caused by the gain of function mutation in the*FGFR3*gene (Pauli, 2019). The *FGFR3*geneen code sfibroblast growith factor receptor 3. The mutated protein result sin hibition of cartila ginous bone growth, causingbonedistortionordisproportionate growth relative tonearbystructures (Webster andDonoghue, 1996). The estimatedprevalenceofthis autosomal dominant diseaseis1 in every 25000-30000 people (Ireland *et al.*, 2014). Most cases are almost confidently diagnosed by mere phenotypic observation without the need for radiological imaging or mutation analysis. Gross physical abnormalities include rhizomelic disproportion, megacephaly, craniofacial deformity, genavarum, brachydactyly and trident configuration of fingers, progressive development of lordosis, redundant folds on the arms (Pauli, 2019). Sufferers are known to report many medical difficulties which can even shorten the expected life span by as much as 10 years, some of which are arthritis, mid-life cardiovascular issues, obstructive sleep apnea, frequent ear infections, hydrocephaly (Pauli, 2019). Although well-known genetic disease, achondroplasia is yet too described for Bangladeshi population. Here, we describe five cases of achondroplasia from Bangladesh based on their phenotype.

CASE 1

The first of the cases that we present would be of a certain Babul Mia, aged over 60 years, height around 3 feet, who is an interesting case of disproportionate dwarfism. Born to an average-height parents, and father to three normal offspring, he is the only individual in his family tree to be afflicted. The most obvious signs would be short, stubby fingers, redundant folds on his arms and the disproportionate stature (Fig. 1A & 2A). Babul Mia spoke of frequent headaches, a lack of fullness to his sleep, joint aches, mild lightheadedness, and limited flexibility to movements. Although his walking is in short strides, he is quite nimble. According to his anecdotal account, he was previously married to a dwarf, now deceased, who died while delivery of their first child; the child died as well at the time.

CASE 2

Hasan Ahmed age 40, also unmarried, does not have a particularly striking family pedigree, born to normal parents. His dwarfism should be obvious in the photograph (Fig 1B), together with bowed legs, and redundant folds on the arms, and abnormal finger growth (Fig. 2B). This individual presented with many medical symptoms, namely, constant shortness of breath, sleep apnea and disturbances, mild back pain, joint aches, dizziness, persistent headaches, and nausea. Interestingly, he also has bilateral developmental cataracts.

CASE 3

Roton Mia Hossain, age of 40 years is the first in his family tree to have the condition. Photographs (Fig 3A) show clearly his short stature, his bowed legs that are disproportionate to his trunk and head, his naturally asymmetric trident configuration (crooked finger) (Fig. 3B) and brachydactyly, an unusually large angle between the feet (Fig 3A), and crowded teeth. He exhibited a normal intelligence and mentioned of no medical difficulties during the enquiry, but we noted a hesitance in his strides as would be expected for someone with abnormal footing. He claims to be unmarried.

CASE 4

MdShahjahan Mia, age of 35, the father of Samiha (Case 5), is discussed separately because he shows different medical symptoms. He is the first child of two normal parents with the condition, and no other ancestors were claimed to have had the disorder. The man shows very prominent craniofacial deformity in his large forehead (Fig 4A), and depressed nasal bridge. He is mildly overweight. He was quite nimble for his stature. However, several bone manifestations of the disorder are clearly present since he complains of limited flexibility at the elbow, limited ability of manual labor, joint aches (arthritis not confirmed) and aches at the neck, severe obstructive sleep apnea. Trident configuration is fairly discernable in the

larger gap between the middle finger and the ring finger, and he has mentioned of faint pain in his finger joints.

CASE 5

Sadia Jahan Samiha, height 2 feet and 5 inches, 9 years old is the second case of achondroplasia. It has been observed that this sufferer is severely restricted in her movements, completely unable to do more than a short-stride walk. She was born with an abnormal large head. Attached photograph (Fig 5A) should also clearly show her bowed legs (genavarum), and the rhizomelic disproportion. However, her normal speech and interactive capabilities and reported school performance are indicative of the absence of hydrocephaly and associated dyslexia. She does complain of frequent headaches. Her fingers clearly exhibit the trident configuration and brachydactyly. At infant-hood she had delayed walking, learning to walk around 3 years old. Samiha never runs, shows very limited elbow extension. She is the only child with this condition, her brother being normal- born to a normal mother, and a father with achondroplasia, who is the subject of the previous case.

Fig. 1. Photographs (not to the same scale) showing rhizomelic disproportion of five subjects; *reduntant folds **bowed legs ***prominently large forehead ****crooked foot.

Discussion

An interesting point to note is the developmental bilateral cataracts in case 5. A concurrence of achondroplasia and cataracts has only once been previously reported in medical literature by *Patil et al.*, who additionally suggested that the causative mutations could be linked on the basis that other ophthalmic conditions are linked to achondroplasia, as are other skeletal syndromes like Hallermann Streiff Francois syndrome and Nance Horan syndrome linked to genetic cataracts (Patil*et al.*, 2017). The "bent" foot presented by case 4, is less commonly described in reports of achondroplasia than are finger deformities. The likelihood of a child inheriting the disorder from an affected a parent and a normal parent is 25%, and yet in 80% of the cases (Orioli *et al.*, 1995), such dwarves are born to parents of average height, as exemplified by most of the cases

that have been presented. The causative mutation is created *de novo* during spermatogenesis and clonal expansion of the mutated cells is the mechanism for positive selection that over time renders an older father more likely to produce an offspring with the condition (Giudicelli *et al.*, 2008). Achondroplasia is described as one the small numbers of RAMP disorders- recurrent, autosomal dominant, male biased, paternal age effect disorder (Yoon *et al.*, 2013).

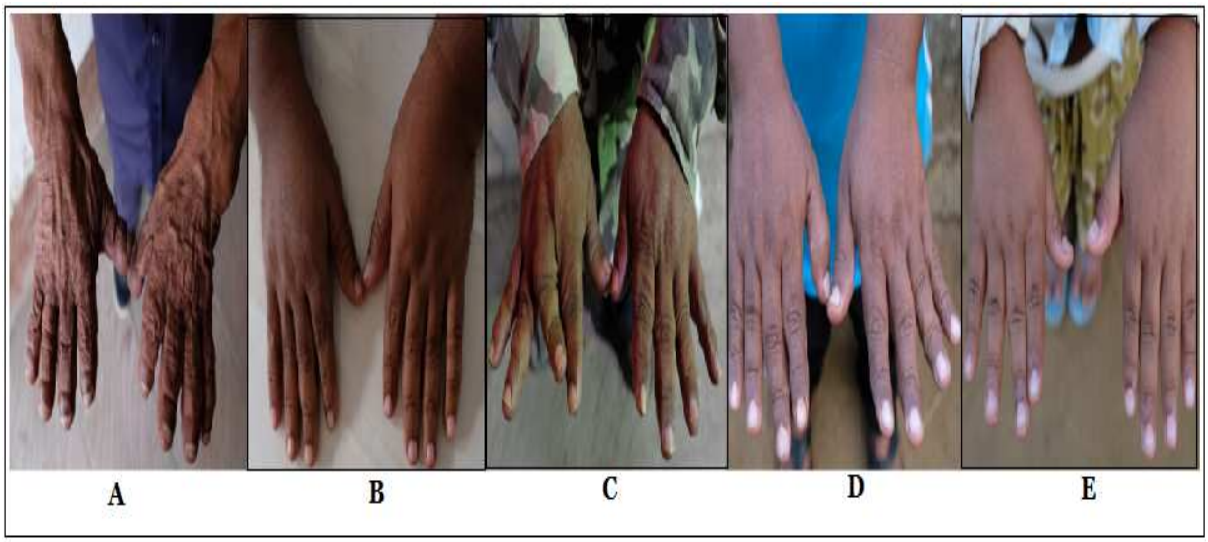

Fig. 2. Photographs showing clear bradydactyly* and trident configuration**; Case 3 with his crooked finger***.

The shared point about all the attempts that have been undertaken by the sufferers listed above is that the patients do not tend to seek medical attention for the symptoms that they suffer from. Learning to live with limited motion and persistent pain, as is the case with all of the patients, is the general attitude.

This apparent negligence may be due to economic status (all of the dwarves thus studied are from working class families), or social stigma or both. Thus, medical reports could not be obtained or examined.

The upbringing of an achondroplasic child carries with it much personal trauma, social issues, and couples may benefit greatly from pre-natal genetic diagnosis and counselling. Targeted prenatal mutation analysis is routinely performed in developed countries to confirm achondroplasia over other dysplasias, also to rule out the possibilities of homozygotes in utero, which is a lethal form of the condition. Although the risk is 25%, a common practice of assortative mating in the dwarfing communities will greatly increase the likelihood of such a case happening (Pauli, 1983).

Conclusion

In summary, achondroplasia seems to be a debilitating disease that clearly lessens the quality of life, and is wrought with suffering that is not heard of in the community. From the ease of obtaining the cases, it is apparent that achondroplasia is not a very rare condition, but certainly not one that has been paid enough attention to in Bangladesh, with sufferers not near-enough receiving the care and support that they may well benefit from. Not surprisingly, there is no cure for this genetic disorder. Good management can and should be attempted in Bangladesh. Recommendations have been put out by American Academy of pediatrics committee on genetics to monitor height, weight, head circumference, using growth curves standardised for achondroplasia, referral to a paediatric orthopedist if bowing of the legs interferes with walking, speech evaluation by age two years, and careful monitoring of social adjustment. Growth has been described as an excellent, nonspecific indication of general well-being well; parents therefore should be accordingly

informed. It is of our observation that families of Bangladesh are unaware of the dangers of conceiving a child by older fathers or that the condition can lead to high-risk pregnancies in women with achondroplasia- as was probably the case with the achondroplasic spouse of Babul Mia (Case 1), although no absolute evidence can be brought to light- or indeed, that it is inherited. More research in the native country is thus required, aimed at locating sufferers, establishment of standard medical diagnosis, treatment and promotion of awareness and of counseling.

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