

Case Report

A rare presentation of KBG syndrome

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ABSTRACT

KBG syndrome is a rare, genetic disorder characterized by cognitive impairment, short stature, skeletal (mainly costovertebral) anomalies and a distinct craniofacial appearance. It is usually autosomal dominant in nature with a wide range of expressivity in its clinical features. We describe what appears to be the third case reported from India. The aim of this article is to review familiar clinical features and to highlight the endocrine management of KBG syndrome. We are hereby reporting a case of 17 year 10 months old adolescent who had neurocognitive impairment and a characteristic appearance, which led to the diagnosis of this genetic condition.

Keywords: KBG syndrome, Short stature, Macrodonia, ANKRD11 gene

INTRODUCTION

KBG syndrome was first described in 1975. The name is derived from the initials of the first three families in which the condition was described.¹ The majority of the individuals are the first in the family to be affected by the condition; although familial cases have been described. There is variable expressivity among and within the families. More males than females with KBG syndrome have been reported. In some families a mildly affected mother is diagnosed only after a typically affected son is recognized.² Features are typically present at birth but may be difficult to recognize until developmental delay is apparent, or permanent teeth erupt. It is likely that this syndrome is less frequently diagnosed since features are not severe and fairly common among other disorders.

CASE REPORT

17 year 11-month-old male adolescent first born child to a second-degree consanguineous marriage presented with complaints of short stature and increased weight gain for 4 months. He was born full term through normal vaginal

delivery with a birth weight of 2.5 kg, with NICU stay for 3 days in view of mild birth asphyxia. The child had delayed developmental milestones and developed seizures at the age of 15 years and was started on antiepileptic drugs (Topiramate, Lacosamide and Clonazepam). He also had history of recurrent ear infections. He had a younger sibling who succumbed to pneumonia at 7 years of age who was also short. The father was also short according to the mother and had expired due to illness, he also had subnormal intelligence according to the mother. There was also history of short stature in three of his paternal aunts. He is presently studying in 7th standard with poor scholastic performance.

On examination his height was 112.8 cm (-7.4 z score), weight was 29.7 kg (-7.03 z score), he had a height age of 6 years and weight age of 8 years 6 months and the target height for the proband was 148 cm (<3rd centile) (Figure 1). His PR- 92/min, RR- 24/min and BP- 96/70 mmHg. His upper segment to lower segment ratio was 0.9. He had a triangular face, brachycephaly, widely spaced eyes, broad eyebrows and thin bow-shaped lips. The upper central incisors appeared to be abnormally large

(Figure 2). The finger nails showed vertical ridges which were not very prominent over the toe nails. Systemic examination was normal and he was pubertal.



Figure 1: He was noted to be short, had a triangular face, brachycephaly, widely spaced eyes, broad eyebrows and thin bow-shaped lips



Figure 2: The upper central incisors appeared to be abnormally large

Complete blood count, liver function test, blood sugars, renal function test, thyroid function test and serum cortisol (6.6 mcg/dl) were normal. Bone age was significantly delayed (13.7 years). Growth hormone test done using clonidine showed a peak growth hormone response of 4.7ng/ml (poor response). On hearing evaluation, he had bilateral mild conductive hearing loss and his assessed intelligence quotient (IQ) was 42. His whole exome sequencing done detected a significant heterozygous non synonymous variation in the exon 9 of ANKRD11 gene on chromosome 16 at a depth of 143 X. This variation causes a change of amino acid tryptophan to cysteine at position 1679. Initiation of growth hormone therapy was advised, which the parents denied.

We could not get the genetic testing of the parents as the father had expired and the mother was not willing due to financial constraints.

DISCUSSION

Craniofacial findings have been reported in 62%-80% of those affected with KBG syndrome. The characteristic facial appearance includes a triangular face, brachycephaly, synophrys with full eyebrows, and widely spaced eyes. A prominent nasal bridge, bulbous nose, anteverted nares, broad or bushy eyebrows, prominent ears, long philtrum, and thin vermilion of the upper lip are also common. The craniofacial findings may not always be apparent; hence a lack of these features does not preclude the diagnosis.³

Macrodonia of permanent upper central incisors is reported in 85%-95% of affected individuals.^{3,4} In addition to macrodonia, shovel-shaped incisors, enamel hypoplasia, hypo/oligodontia, dental pits, dental crowding, large dental pulps, and supernumerary mamelons can be seen.^{3,5} KBG syndrome is caused by mutations in the ANKRD11 gene located on chromosome 16q24.3, which encodes an ankyrin repeat domain-containing cofactor.^{6,7} Over 110 cases have been reported in the literature so far.⁸ A very few cases of KBG syndrome have been reported from India to the best of our knowledge.^{9,10} ANKRD11 is expressed in the brain and localizes mainly to the nuclei of neurons and glial cells.¹¹ ANKRD11 has two transcription repression domains and a transcription activating domain. The protein regulates ligand dependent transcriptional activation through recruitment of histone deacetylases to the p160 coactivators/nuclear receptor complex. ANKRD11 was found to be a novel p53-interacting protein improving the transcriptional activity of p53, hence functioning as a p53 coactivator.^{12,13}

A new diagnostic criterion for KBG syndrome was composed by Low et al.³

The major criteria included: 1) macrodonia* (85%) 2) height below the 10th centile* (66%) 3) recurrent otitis media and/or hearing loss (44%) 4) 1st-degree relatives with KBG syndrome* (22%).

The minor criteria included: 1) Brachydactyly (50%), 2) seizures* (43%) 3) cryptorchidism (31%) 4) feeding problems (34%) 5) Palate abnormality (25%), 6) autism(24%) 7) delayed closure of the anterior fontanelle (22%) *Criteria present in our case

A diagnosis of KBG syndrome should be considered in a patient with developmental/ learning difficulties, speech delay or significant behavioural issues with at least two major criteria or one major and two minor criteria.

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delay or significant behavioural issues with at least two major criteria or one major and two minor criteria.

The incidence of short stature in KBG syndrome is relatively high. The effects of growth hormone (GH) therapy on children with KBG syndrome accompanied by short stature are not clear. In a study done by Ge et al the data of children with KBG syndrome accompanied by short stature was collected.¹⁴ A total of ten children with KBG syndrome accompanied by short stature who received GH therapy were included. Height SDS improved in nine (9/10) children with KBG syndrome accompanied by short stature after GH therapy.

Available data suggests that ANRCD11 gene mutation does not seem to limit a response to exogenous growth hormone treatment during childhood.

CONCLUSION

In conclusion the management of KBG syndrome requires a multidisciplinary approach. Treatment involves speech therapy for palatal anomalies; nasogastric tube feeding in infants; pharmacologic treatment for gastroesophageal reflux disease; pressure-equalizing tubes and/or tonsillectomy/adenoidectomy for chronic otitis media; consideration of amplification for hearing loss; consideration of growth hormone therapy for short stature and medication to arrest puberty for premature pubertal development; standard treatment of seizure disorder, undescended testis in males, congenital heart defects, strabismus/refractive errors and developmental disabilities.

Growth hormone therapy for short stature and medication to arrest puberty for premature pubertal development should be considered. Short stature is prevalent in patients with KBG syndrome and spontaneous catch-up growth beyond childhood appears limited. Intervention in the form of growth hormone therapy in KBG syndrome children is perceived as promising and warrants further exploration.

By reporting this case we emphasize the role of genetics in a case of short stature with neurocognitive delay as a genetic diagnosis will aid us in choosing the appropriate therapy.

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