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KBG Syndrome: A Rare Genetic Disorder

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ABSTRACT

KBG syndrome is a rare autosomal dominant genetic disorder caused by mutations in the ANKRD11 gene located at 16q24.3. This syndrome is present at birth and is characterized by a wide range of clinical features, including distinctive facial dysmorphisms, developmental delays, skeletal abnormalities, dental issues, and cognitive deficits. Diagnosis is challenging due to the rarity and variable presentation, requiring a combination of clinical evaluation, genetic testing, and imaging studies. Although there is no cure, early intervention and support can improve the individual's quality of life. This article reviews the clinical features, diagnostic criteria, management strategies, and prognosis of KBG syndrome, highlighting the importance of accurate diagnosis and comprehensive care.

Keywords: KBG syndrome, ANKRD11 gene, genetic testing, developmental delays, skeletal abnormalities, genetic counselling.

INTRODUCTION

Nestled within the intricate genome, KBG syndrome emerges as an exceptional autosomal dominant disorder, evoking profound developmental consequences from the very inception of life. This unique genetic anomaly stems from a mutation localized in the ANKRD11 gene residing at the precise chromosomal locus of 16q.24.3. This mutation, in turn, orchestrates a perturbation in the structural integrity of the scaffolding protein within this genomic region, leading to a shortened variant. This molecular diminution exhibits a spectrum of functionality, ranging from complete efficacy to partial operation, thereby bestowing the intricate and variable symptomatology that characterizes KBG syndrome.

EPIDEMEOLOGY:

KBG syndrome was first described in 1975 by Herrmann et al as a new malformation or retarded syndrome in three families and the name came from the initials of those families. Males are more affected almost twice than females. Milder in females. It has been reported in Egypt, Australia, Italy, India and more countries.

By the end of 2004, 29 patients were reported with KBG syndrome. According to a paper KBG syndrome – "By Brancate, Sarkozy and Daliapiccola in 2006, 49 patients were identified with this syndrome". In 2015, 32 patients with KBG syndrome were genetically confirmed.

ETIOLOGY:

KBG syndrome is caused by mutations in ANKRD11 at location 16q.24.3. The protein produced from that gene enables other proteins to interact with each other and helps to control gene activity. The ANKRD11 protein is it found in nerve cells in the brain, it may function in other cells in the body and appears to be involved in normal bone development. So, mutation in their gene causes neurodevelopmental disorders, abnormal skeletal development.

Their condition is an inherited autosomal dominant pattern.

Clinical Features:

- Macrodontia: This refers to abnormally large teeth, which can affect both primary (baby) and permanent teeth. It can lead to dental issues, including misalignment.
- Oligodontia (Absence of more than 6 teeth): Oligodontia is the congenital absence of more than six teeth, which can impact dental development and oral health.
- Facial dysmorphisms: Individuals with KBG syndrome often have distinctive facial features, such as a triangular face, a prominent forehead, widely spaced eyes, and a prominent nasal bridge.
- Branchy – clinodactyly (5th finger short or curved): Branchy-clinodactyly refers to a specific type of finger abnormality, where the fifth finger (pinky finger) is shorter or curved, which can be noticeable on physical examination.
- Webbed / short neck: A webbed or short neck is a condition in which the skin of the neck is thicker or extends more towards the shoulders, or the neck itself is shorter than usual.
- Cognitive deficient/psychomotor delay: Cognitive deficiencies and psychomotor delays refer to intellectual and developmental challenges, including learning difficulties and delayed milestones in areas such as walking and talking.
- Cryptorchidism: This is a condition in males where one or both testicles do not descend into the scrotum as expected. It's a common feature in KBG syndrome.
- Abnormal spinal curvature: This may involve scoliosis (sideways curvature) or other spinal abnormalities, which can affect posture and mobility.
- Hearing loss: Hearing loss is a potential feature of KBG syndrome and can vary in severity. It may require management such as hearing aids.
- Short stature: Individuals with KBG syndrome may have a height below the average range for their age and gender.
- Palatal defects: Palatal defects include issues with the roof of the mouth, such as cleft palate, which can affect speech and eating.
- Abnormal EEG with seizures: An abnormal electroencephalogram (EEG) along with seizures is a neurological feature that some individuals with KBG syndrome may experience.
- Congenital heart defects: Some individuals with KBG syndrome may have heart abnormalities present from birth, which may require medical attention.
- Strabismus: Strabismus is a condition where the eyes do not align properly and may point in different directions. It can impact vision.
- Prominent or anteverted ears: "Prominent" refers to ears that stick out more than usual, while "anteverted" means that the ears are rotated forward.
- Cutaneous syndactyly, toes: Cutaneous syndactyly refers to webbing of the skin between toes. It's a relatively common finding in KBG syndrome.

It's important to note that the severity and specific combination of these features can vary widely among individuals with KBG syndrome.

DIAGNOSTIC CRITERIA:

Four cardinal malfunctions may be outlined that includes facial dysmorphism, macrodontia of the upper central incisors, skeletal (mainly costovertebral) anomalies and developmental delay. The diagnostic criteria for KBG Syndrome were previously reported by Smithson et al in 2000.

Diagnosis of KBG syndrome includes major and minor criteria.

MAJOR CRITERIA:

- Facial dysmorphisms.
- Macrodontia.
- Skeletal abnormalities.
- Cognitive deficits/psychomotor delay.

- Short stature.
- Abnormal EEG.
- Abnormal hair implantation

MINOR CRITERIA:

- Cutaneous syndactyly, toes 11/111.
- Webbed/short neck.
- Cryptorchidism.
- Hearing loss.
- Congenital heart defects

Two major or one major and two minor criteria confirm the diagnosis.

MANAGEMENT:

KBG syndrome is a genetic disorder for which there is no specific cure. However, management focuses on addressing the various manifestations and improving the individual's overall quality of life.

1. Feeding Issues and Dieticians: It's essential to address feeding difficulties, especially in infants and young children with KBG syndrome. Consulting a registered dietitian can help ensure proper nutrition, manage feeding challenges, and promote healthy growth. Dietitians can provide guidance on appropriate diets, feeding techniques, and may recommend nutritional supplements if needed.

2. Therapies:

Speech Therapy: Many individuals with KBG syndrome may have speech and language delays. Speech therapy can help improve communication skills, enhance speech articulation, and address language challenges.

Behavior Therapy: Behavioral issues, such as attention deficits and social difficulties, may be present. Behavior therapy, including applied behavior analysis (ABA) or other behavioral interventions, can help manage these challenges and improve social interactions.

Occupational Therapy: Occupational therapy focuses on enhancing fine motor skills, sensory processing, and activities of daily living. It can be beneficial for individuals with KBG syndrome who have motor delays or sensory sensitivities.

3. Genetic Counseling: Families affected by KBG syndrome can benefit from genetic counseling. Genetic counselors can provide information about the inheritance pattern of the syndrome, discuss the likelihood of recurrence in future pregnancies, and offer emotional support to families.

4. Special Education Services: Many individuals with KBG syndrome may require specialized educational support. Enrolling the affected individuals in special education programs tailored to their needs can help maximize their learning potential.

5. Regular Medical Checkups: Due to the multisystem nature of KBG syndrome, regular medical evaluations are crucial. These checkups help monitor the individual's overall health, identify any new issues, and ensure timely intervention.

6. Orthopedic Evaluation: Given the potential for skeletal abnormalities, an orthopedic evaluation can be beneficial to monitor and manage issues such as scoliosis or other spinal abnormalities.

7. Hearing and Vision Assessments: Regular hearing and vision assessments are important, as hearing loss and vision problems are common in KBG syndrome. Appropriate interventions, such as hearing aids or corrective lenses, can be recommended.

8. Seizure Management: For individuals with abnormal EEG and seizures, a neurologist's involvement is essential. Medications and seizure management strategies can be prescribed to improve the individual's quality of life.

9. Support and Advocacy Groups: Connecting with support and advocacy groups for rare genetic disorders can provide families with valuable resources, emotional support, and opportunities to share experiences with others facing similar challenges.

10. Individualized Care: Each individual with KBG syndrome is unique, and their care should be tailored to their specific needs and challenges. A multidisciplinary approach involving medical specialists, therapists, educators, and caregivers is

crucial to providing comprehensive care and support.

INVESTIGATIONS:

1. Molecular Testing - ANKRD11: This is a crucial step in confirming the diagnosis of KBG syndrome. DNA sequencing of the ANKRD11 gene is performed to identify pathogenic variants (mutations) that are associated with the syndrome. This can involve looking for intragenic variants (point mutations or small insertions/deletions) within the ANKRD11 gene.
2. Echocardiogram: An echocardiogram is used to assess the heart's structure and function. It helps detect congenital heart defects, such as ventricular septal defects (VSDs), bicuspid aortic valve, and other abnormalities. This evaluation is important, as some individuals with KBG syndrome may have associated heart defects.
3. EEG (Electroencephalogram): An EEG is a test that measures the electrical activity of the brain. Nonspecific EEG anomalies are observed in a significant percentage of individuals with KBG syndrome, and around 25% of them may develop seizures. An EEG can help identify abnormal brain activity and guide seizure management if necessary.
4. Audiometry: Audiometric testing assesses hearing sensitivity. Hearing loss is a common feature in KBG syndrome, affecting approximately 20-31% of reported individuals. Recurrent otitis media (ear infections) has been associated with hearing loss in some patients with KBG syndrome. Audiometry helps quantify hearing impairment and guide interventions, such as hearing aids if needed.
5. Genetic Analysis:

Single Gene Testing: Initially, sequence analysis of the ANKRD11 gene is performed to look for point mutations or small genetic changes within the gene.

Deletion/Duplication Analysis: If no pathogenic variant is found in the sequence analysis, additional testing may involve gene-targeted analysis to detect larger deletions or duplications within the ANKRD11 gene.

PROGNOSIS:

The prognosis for individuals with KBG syndrome can vary widely based on the specific features and severity of the syndrome in each case. Since KBG syndrome is a rare disorder, there is limited information available, and the long-term outcomes can be influenced by many factors. Here are some general points to consider regarding the prognosis:

Variable Severity: The severity of KBG syndrome can range from mild to more significant. Some individuals may have only a few of the characteristic features, while others may experience a broader range of symptoms. The impact of specific manifestations (e.g., intellectual and developmental delays, skeletal abnormalities, hearing loss) on an individual's overall quality of life can vary.

Intellectual and Developmental Challenges:

Many individuals with KBG syndrome may experience cognitive and developmental delays. The extent of these delays can influence the individual's educational and vocational opportunities. Early intervention, therapies, and educational support can play a crucial role in helping individuals reach their fullest potential.

Medical Complications: Certain medical complications associated with KBG syndrome, such as heart defects or seizures, may require ongoing medical management. With appropriate medical care, these complications can often be addressed effectively, improving the individual's overall health and well-being.

Lifespan: KBG syndrome itself is not typically associated with a significantly shortened lifespan. Individuals with KBG syndrome can lead fulfilling lives, especially with appropriate medical care and

support from a multidisciplinary team of healthcare professionals.

Quality of Life: The quality of life for individuals with KBG syndrome can be positively influenced by early diagnosis, access to appropriate medical care, therapeutic interventions, and supportive educational and social environments. Addressing specific challenges, such as speech and communication difficulties, can significantly improve the individual's ability to interact with others and participate in daily activities.

Differential Diagnosis

Several genetic syndromes share overlapping clinical features with KBG syndrome, making a differential diagnosis essential. Conditions that may be considered in the differential diagnosis include:

Kabuki syndrome: Most cases of Kabuki syndrome are caused by mutations in two genes: KMT2D (also known as MLL2) and KDM6A. These genes are involved in epigenetic regulation and chromatin remodeling. Facial dysmorphisms like Long palpebral fissures (longer eye openings), arched eyebrows, depressed nasal tip, and prominent ears. Developmental delays, Skeletal abnormalities and Cardiac abnormalities are also seen.

Coffin-Siris syndrome: Mutations in several other genes, including ARID1A, SMARCB1, SMARCA4, and others, can cause Coffin-Siris syndrome. Similar features, including developmental delays and intellectual disability. This syndrome is differentiated with its distinct facial features, hirsutism and Fifth Finger and Toe Abnormalities.

Wiedemann-Steiner syndrome:

Wiedemann-Steiner syndrome is primarily caused by mutations in the KMT2A gene, which is also known as MLL1. KMT2A is involved in epigenetic regulation and chromatin remodeling. Overlapping craniofacial features and developmental delay with KBG syndrome.

Cornelia de Lange syndrome: Mutations in the NIPBL gene are the most common cause of Cornelia de Lange syndrome. NIPBL is involved in sister chromatid cohesion and gene regulation. Upper Limb Anomalies like small hands with fifth finger clinodactyly (curved pinky finger) and absent or underdeveloped forearm bones are seen. They also have distinctive facial features and intellectual disabilities.

CONCLUSION

KBG Syndrome remains underdiagnosed. KBG syndrome is a rare genetic disorder with a variable presentation of clinical features, often involving facial dysmorphisms, developmental delays, dental issues, and skeletal abnormalities. Early diagnosis through molecular testing of the ANKRD11 gene, along with comprehensive clinical evaluation, is crucial for appropriate management and genetic counseling. While there is no specific cure, a multidisciplinary approach involving therapies, regular medical checkups, and support services can significantly improve the quality of life for individuals with KBG syndrome. Further research and advancements in understanding the underlying genetic mechanisms of the syndrome may lead to improved diagnostic techniques and targeted interventions in the future.

Declaration by Authors

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