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Case Report

Kbg Syndrome: Report of Musculoskeletal Motor Affection and Review of the Literature

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Abstract

Introduction: KBG syndrome is a rare autosomal dominant disorder. There are about 100 cases published in the literature. The most consistent shared characteristics are macrodontia, distinctive craniofacial findings, musculoskeletal abnormalities and development delays. Mutations in the ANKRD11 gene were identified in most patients and is an important diagnostic tool.

Materials and methods: We report a 16 years old boy with any interesting family background. He was evaluated by multiple specialist for multiple problems like transmission hearing loss, inguinoscrotal hernia, micrognathia, low set ears, large incisors, ogival palate…On the musculoskeletal field he has hypertonia, small hands and fingers on drumstick and a hip dysplasia since breastfeeding which was treated with Pavlik cast with good results. On the lower extremities we found asymmetric legs, bilateral knee flex and equine tendency, similar findings that those we found on PCI patients.

Results: With all the findings, we send our patient to the Regional Reference Unit for Advanced Diagnosis of Rare Paediatric Diseases of Castilla y León. They have studied the ANKRD11 gene, with heterozygous result.

Conclusions: To our knowledge, this is the first case reported in the literature giving importance to the musculoskeletal affectation in the KBG syndrome. We think that some of the features and restrictions we find in this patient are similar that those we can see in PCI, and the GMFM could be a great tool to measure and guide the treatment of this patients.

Keywords: Gross motor; KBG; Rare disease

Abbreviations: GMFM: Gross Motor Function Measure; EEG: Electroencephalogram; ADHD: Attention Deficit/Hyperactivity Disorder; GH: Growth Hormone; NGS: Next Generation Sequencing; CK: Creatinine Kinase; PCI: Children Cerebral Palsy; IGF-1: Insulin Like Growth Factor 1; TNN: Tenascin N; aCGH: Microarray Based Comparative Genomic Hybridization; IGFBP-3: Insulin Like Growth Factor Binding Protein 3; ANKRD11: ankyrin Repeat Domain 11

Introduction

KBG syndrome is a rare autosomal dominant disorder, typically with more severe findings in males [1]. There are about 100 cases published in the literature. It was firstly described by Hermann et all in 1975 [2], in seven patients from three unrelated families with surname initials K, B and G.

The most consistent shared characteristics are macrodontia, distinctive craniofacial findings, musculoskeletal abnormalities, post-natal short stature, and development delays. There are other

characteristics which are common, like EEG abnormalities, hair findings, delayed bone age, digital anomalies, Attention Deficit/ Hyperactivity Disorder (ADHD), autistic like behaviour, etc. [1,3].

Mutations, indels, and large deletions in the ANKRD11 (Ankyrin Repeat Domain 11) gene were identified in most patients [4]. Deletions in 16q24.3 gave similar findings to those with intragenic variants, but also have a higher incidence of other findings such as brain anomalies, congenital heart defects, severe astigmatism, thrombocytopenia, and potentially autism spectrum disorder among other behavioural problems [1].

ANKRD11 was initially hypothesised as a tumour suppressor gene. It's overexpression inhibits transcriptional activation in vitro [5]. The transcriptional regulatory domains of the protein include two repressor domains at the N and C termini and an additional activation domain [6]. The ANKRD11 protein is highly expressed in the human brain and localized to nuclei of neurons and glial cells [7]. This domain influences the expression of several genes related to neural development, highlighting its association with the neurobehavioral and developmental phenotype in KBG syndrome [8]. Similarities between the 16q24.3 microdeletion syndrome and KBG syndrome suggest that these are overlapping entities mediated by ANKRD11 haploinsufficiency [9].

Results from the DDD triome study at United Kingdom found that mutations in ANKRD11 accounted for around 1% of patients with an undiagnosed developmental delay [10], so we can hypothesize that KBG syndrome is still an under-recognized clinical condition.

We report the case of a 16 years old boy who was evaluated in our orthopaedic surgery and traumatology consultation.

Case Report and Clinical Description

Our patient was evaluated the first time in 2007 due to short-stature. He was born at 37 weeks of gestation, birth weight was 2460g and 46 cm high. He was given birth by caesarean, because of breech birth, with a 9-10 Apgar test.

His family background shown: mother with 151,5 cm high, father with 173,4 cm high and a ten years old sister with 129,4 cm high. Maternal menarche at the age of twelve. Without any other interesting familiar pathology.

Patient underwent to multiple medical examination from different specialists: discharged from Cardiology for a septal defect without hemodynamical repercussion; followed-up from Endocrine for retractile testicle and underwent Otorhinolaryngology surgery for congenital loss hearing transmission. He was operated too due to inguinoscrotal hernia and phimosis. Psychology evaluation shown intelligence quotient of 62.

As orthopaedic surgeons we´d evaluated the child with regard to multiple muscular contractures and hip dysplasia since breastfeeding, which was treated with hip abductor casts like Pavlik. In progressive evaluations we can see delayed bone age but pubertal advance. It's important to remark in physical exploration we noticed narrow frontal bone, low set ears, micrognathia, large incisors, ogival palate and pterygium colli. He had apparently muscular generalized hypertonia, small hands, fingers as drumstick and clinodactyly of the fifth finger. Arms are symmetrically shortened, and he has a limitation on the prone-supination. In 2016, at the age of 13, lower limbs were asymmetric less than 1cm, bilateral knee flexion < 10° was noticed but normal hip mobility was achieved.

In 2018 gait analysis was very deteriorated. He had crouched gait, with plantigrade foot but bilateral equine tendency. Right knee flexion is about 15 degrees and 10 degrees in left side. Bilateral dorsal flexion of ankles was about 95 degrees. Negative Silfverskiöld test. Positive Galeazzi test about 8mm. Hip abduction was about 50 degrees bilateral. Patient was treated with botulinum A-toxin at the Achilles tendon in June 2018. On the next evaluation the Silfverskiöld test was positive bilaterally, and the rest of the evaluation was similar than previous.

At this moment our patient has been realized a karyotype (XY), celiac test which is normal, IGF1 and IGFBP3 (firstly on inferior limits), study of genes TNN12 and TNN13 (normal), GH test (normal), NGS for Noonan syndrome and arthrogryposis (normal), normal aCGH Arrays, normal CK and NGS for bone dysplasia (normal). In 2013 a bone series is requested. We found lumbar vertebrae with anterior notch, irregular saucers, bilateral floating ribs with accessory rib above D1. D2 and D3 apparently fused. In upper limbs we found radio ulnar disparity with small hands and phalanges, and clinodactyly of the fifth finger.

Materials and Methods

With all the findings we have, we send our patient to the Regional Reference Unit for Advanced Diagnosis of Rare Pediatric Diseases of Castilla y León. They have studied the ANKRD11 gene, with heterozygous result. As said in the introduction, this variant has been reported as pathogenic in multiple individuals with KBG syndrome [9]. It provokes a change in the lecture between the 635 Lys codon to glutamine, and it induces a stop codon in the p.Lys635GlnfsX26 position. The consequence is a protein loss because a truncated protein or an alteration of the mRNA.

This variant is not observed in wide cohorts of general population [11]. For all this, the variant is considered according to ClinVar as a pathogenic variant.

Results

This case is the first reported in literature giving importance to the musculoskeletal affectation in KBG syndrome. Some of the features where previously described in other patients with KBG, like

hip dysplasia [1], delayed bone age or clinodactyly. Others where less commonly described in this syndrome. Our patient has similar musculoskeletal findings that those seen in children cerebral palsy (PCI) [12]. Cerebral palsy describes "a group of disorders of the development of movement and posture causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, cognition, communication, perception and/or behaviour and/or a seizure disorder" [13]. The most commonly form of this disease is the spastic affectation characterized with continuous contraction of certain muscles. This contraction causes stiffness or tightness of the muscles and can interfere with normal movement, speech and gait. The affection pattern could be an hemibody (hemiplegic/paretic), one-limb (monoplegic/paretic), two-limb (paraplegic/paresic) or four-limb (tetraplegic/paresic).

In PCI patients, is very extended the use of the GMFM-88 and GMFM-66 as a tool to measure gross motor function. These tools allow us to know the motor index for the gross function, to establish a forecast to the rehabilitation, and to value the degree of improvement of the motor function in children who are involved in a treatment plan. The GMFM was published firstly in 1990, thanks to the work of Pallisano with his motor development curves, classifying children according to their severity. Today is widely used in clinical practice and investigation.

The GMFM-88 consists in 88 items, grouped in 5 different fields of gross motor function:

- Supine and rolled.
- Sitting
- Drag, down on knees and crawl.
- Standing.
- Walk, run and jump.
- Optional item: help and orthosis test.

You need to register how much the child achieves in each item, not how well do execute the activity. The original scale was validated in children between 5 and 16 years old. Every item can be completed by a normally developed child.

The GMFM – 66 is a more recent version with 66 items. Is formed by a subset of the 88 items of the anterior classification.

There are four points in the classification system to each item, which are the same for the two versions.

- 0 = the movement is not initiated.
- 1 = is initiated, but the child can complete only < 10% of the task.
- 2 = partially completed, >10% but <100%.
- 3 = completed. 100%.
- NE = no evaluated. Item not applied, it can't be done, or the child rejects the activity, even when he shows skills to play it at least partially. The punctuation of this item is 0.

The estimated time to the application of the GMFM-88 is about 45-60 minutes, depending on the evaluator abilities, and the comprehension, collaboration and functionality of the child. The application of the GMFM-66 may be faster, according to the smaller number of items.

The final punctuation is made by the sum of the scores in each of the five fields, and them the calculation of the percentage in each one of the five fields (child score / maximus score) x 100, and them we calculate the average of the scores. Finally, we classify the score in five levels, according to the child age:

- Level 1: the child walks without restrictions; has limitations in complex motor skills.
- Level 2: the child walks without help devices; has limitations outdoors and in the community.
- Level 3: child walks with help devices, has limitations outdoors and in the community.
- Level 4: autonomous displacement but with limitations; he is transported or neds self-propelled wheelchair.
- Level 5: very limitated self-displacement even with self-propelled technology.

Although the scales were designed for PCI children, there's evidence that we can use the GMFM-88 to Down syndrome patients. When it comes to a scale based in the execution of the typical motor abilities in the children development, it can be useful in other population groups with different syndromes.

This scale is very useful to measure the changes in gross motor function in children undergoing interventions. This was studied in a revision of PCI patients [13].

In our boy we can see at the age of fifteen, bilateral knee flex (15 degrees on the right side and 10 degrees on the left side), equine tendency with 95 degrees of dorsal ankle flexion, and negative Silverskiold test. He has 8mm of discrepancy between the two legs in the Galeazzi test and 50 degrees of hip abduction. He was treated with botulinum toxin in the Achilles tendon with improvement in the Silverskiold test. He was in the level one of gross motor function, walking without restrictions, and he didn't need any surgical intervention in this moment.

Discussion

In this paper we describe the clinical aspects of our KBG patient. This is a rare disorder with only a hundred cases reported

before 2017 [1], and since that time to our days only seven papers talk about new patients [14-20].

There are common aspects which were reported in previous cases, like macrodontia, triangular face, thin upper lip, developmental delay, EEG abnormalities, cryptorchidism…[1]. These features will facilitate its clinical diagnosis, but it should be confirmed by a genetical study of the ANKRD11 gene. It's important to know that the absence of the mutation does not exclude the diagnosis [1]. We can find patients with a clinical diagnosis of KBG and missing variants in ANKRD11 or in additional genes. Further studies will help delineating the spectrum of phenotypes, details of ANKRD11 function and dysfunction in KBG syndrome.

Some of the findings we describe were related to the musculoskeletal aspect, like bone age delay, costovertebral anomalies, scoliosis… [21], but there is not any information about the ability of children to face their daily routines according to their musculoskeletal limitations. It's known that they sometimes have brachydactyly [14], clinodactyly or hip dysplasia [1], but there's not any paper talking about how this affect to their movement or ability to handle objects, what is much more important for their daily life and the aids they need.

We focus our case in the musculoskeletal aspects of this rare syndrome, cause there's not much information about it. We think that these abilities can be measured with the GMFM, because the features and restrictions we find in these patients are similar that those we can see in PCI, and as we have previously seen, it has already been used to evaluate other types of patients.

This tool can help us to make the decision if our patient requires some kind of intervention for our part, either physiotherapy treatment, surgical treatment or any other, according to the patient capacity to face his daily routines. We believe that, just like in the PCI, what´s really important in these patients are not its specific limitations in range of motion of any joint, or its fingers deformities, but what those deformities involve in their lives. The GMFM it's a proven tool to give us that information.

That´s why we have used the GMFM scale in this case and we propose it as a very useful tool both in the initial evaluation and in the follow-up of the KBG syndrome.

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The authors declare that they have not any conflict of interest in this paper.

*This study was carried out in Salamanca University Hospital.

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