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Case Report

Witteveen-Kolk syndrome with hypogonadotropic hypogonadism - a diagnostic challenge in syndromic delineation

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ABSTRACT

Witteveen–Kolk syndrome (WITKOS) is a rare neurodevelopmental disorder characterized by developmental delay or intellectual disability, behavioural disorders including autism spectrum disorders, obsessive–compulsive behaviours as well as attention deficit hyperactivity disorder symptoms. It also presents with facial dimorphisms and short stature. The syndrome is caused by loss of function of switch-insensitive 3 transcription regulator family member A (SIN3A). We report a novel case of WITKOS presenting with hypogonadotropic hypogonadism along with neurological manifestation. The need of early diagnosis and anticipation of subsequent manifestations of the syndrome during childhood along with a multidisciplinary approach to treatment has been emphasized.

Keywords: Witteveen-Kolk syndrome, Hypogonadotropic, Hypogonadism

INTRODUCTION

Witteveen-Kolk syndrome (OMIM 613406) is caused due to heterozygous loss-of-function (LOF) variants in switch-independent 3 transcription regulatory family member A (SIN3A) (OMIM 607776) or 15q24 microdeletions encompassing SIN3A. The SIN3A gene is located on the chromosome 15 band q24 and is within the shortest region of overlap of various reported 15q24 microdeletions. It is therefore thought to be the critical gene for the atypical 15q24 microdeletion syndrome.[1] WITKOS is inherited in an autosomal dominant manner and majority of patients are sporadic with haploinsufficiency of the SIN3A gene being responsible for this syndrome.[2] The protein encoded by the SIN3A gene interacts with the transcriptional gene regulation complex associated with scaffolding in the core histone deacetylase complex.[3] involving repress or activate diverse gene targets in a context-dependent manner. It plays a regulatory role in the control of various developmental processes such as cell proliferation, energy metabolism, organ development, and cellular senescence.[4]

WITKOS was first described in 2016 by Witteveen et all characterized by a broad spectrum of neurological and physical phenotypes. Patients have characteristic distinctive facial dysmorphisms, microcephaly and short stature. Additionally, abnormalities in growth, skeletal structure, hearing, visual disorders, gastrointestinal function, and ectodermal features have also been documented in patients with WITKOS.[5] Early or late signs of congenital hypogonadotropic hypogonadism, such as micropenis, cryptorchidism, or pubertal delay, have only been reported in patients with 15q24 microdeletions.[6]

SIN3A is a key regulator of cortical expansion and maturation and its mutation thus results in various degrees of intellectual disability, neurodevelopmental disorders, behavioural problems with delayed cognitive

and motor development and subtle anomalies on MRI-brain imaging.[2]

CASE REPORT

A male child in his early adolescence was brought to a tertiary care hospital with parental concern of bilateral undescended testis. The child is a first product of a non-consanguineous marriage, spontaneous conception, born full term via normal vaginal delivery with low birth weight (2.25 kg) and no history of any adverse antenatal or peri-natal events.

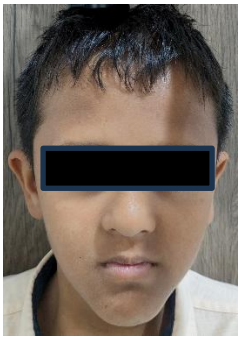

Figure 1: Facial features of Witteeven-Kolk syndrome depicting triangular facies with a short filtrum with microstomia and a pointed chin.

Developmentally, the child attained gross motor and fine motor milestones as per age and was walking by 1 year of age. The child was enrolled in school at 4 years of age however developed scholastic backwardness. He does not have any family history of neurological disorders or intellectual disability.

On examination, the child had undescended testis on the right side and retractile testis on the left side with short penile length of 2.6 cm and was pre-pubertal as per Tanner staging. The child underwent right open orchidopexy at 13 years of age with left testicular fixation and intra-operative findings revealed bilaterally small hypoplastic testis (right > left) The child had dysmorphic facial features in the form of a triangular facies with microbrachycephaly, a narrow brow region, hypoplastic palpebral fissures with ectopia puncta, fanning of ears with fleshy earlobes. He also has a short filtrum with microstomia, crowded dentition and a pointed chin (Figure 1).

Looking at the skeletal features, a long neck and palms with long slender fingers and clinodactyly were observed. Bilateral feet had helix valgus deformity and a sandal gap. Additionally, mild pectus carinatum and exaggerated lumbar lordosis were also found.

Investigations

The child was evaluated for delayed puberty and found to have hypogonadotropic hypogonadism with low levels of gonadotropins (FSH 0.26 mIU/ml, LH less than 0.12 mIU/ml) and low levels of testosterone, Inhibin B and Insulin like growth factor 1. Growth hormone levels were found normal in the growth hormone stimulation test (Table 1). His weight and height corresponded to the 3rd centile as per WHO growth chart with delayed bone age corresponding to 11.3 years.

Table 1: Laboratory evaluation of hypogonadotropic hypogonadism.

Test	Values	Normal range
FSH	0.26	1.2-15.4 mIU/ml
LH	<0.12	1.2-7.8 mIU/ml
Serum testosterone	<12.98 ng/dl	142.39-923.14 ng/dl
IGF1	91.1 ng/ml	180-850 ng/ml
Inhibin B	24.6 pg/ml	47-380 pg/ml
Growth hormone stimulation test	Basal - 0.104 ng/ml, 60 minutes post stimulation - 12.1 ng/ml, 120 minutes post stimulation - 1.67 ng/ml	0.1-7.9 ng/ml

The child was clinically evaluated and found to have delayed cognitive development and scholastic backwardness. On genetic evaluation, whole exome sequencing showed a heterozygous nonsense variant in exon 6 of the SIN3A gene (chr15:g.75411545G>A) (OMIM 607776) that resulted in a stop codon and premature truncation of the protein at codon 319 (p.Gln319Ter; ENST00000394947.8) was detected. It was reported to be 'likely pathogenic' confirming the diagnosis of Witteeven Kolk syndrome (OMIM 613406).

Differential diagnosis

Hypogonadotropic hypogonadism may occur isolated or in association with anosmia or hyposmia, known as Kallmann syndrome.[7] The advent of genetic sequencing techniques has led us to the understanding of the genetic basis of hypogonadotropic hypogonadism in patients with other complex syndromes, such as CHARGE syndrome due to *CHD7* variants, Waardenburg syndrome associated with *SOX10* mutations, TUBB3 syndrome due to *E410K* mutation in *TUBB3* and Pallister–Hall syndrome caused by mutations in *GLI3*.[8,9]

Treatment

WITKOS presenting with mild intellectual disability can often be missed in the early years. An early etiologic diagnosis by identifying clinical symptoms early and initiating rehabilitation interventions are crucial for improving a child's development and quality of life. Multidisciplinary approach involving a team of

specialists, including neurologists, ophthalmologists, endocrinologist and developmental therapists is needed. Physical and speech therapy can help address motor skill delays and communication difficulties. Early intervention for psychiatric and behavioral issues during the developmental period is crucial for achieving optimal outcomes. Specialized training in social skills can support social and emotional development. Regular screening for congenital cardiac or renal defects is recommended. Based on individual needs, pharmacological treatment may be required to manage conditions such as gastroesophageal reflux, gastrointestinal motility disorders, or seizures.

From an endocrinological perspective, monitoring growth and the onset of puberty significantly influences quality of life and social adjustment, particularly in relation to the development of secondary sexual characteristics, adult height, and sexual maturity. In males with hypogonadotropic hypogonadism, features such as cryptorchidism and micropenis may indicate delayed puberty, yet they can remain undiagnosed without targeted evaluation. Growth hormone therapy may be considered, especially in cases involving growth hormone deficiency.

Treatment plans should be tailored to the specific needs of each individual and regular monitoring of development and health is essential to adjust treatment plans as needed. Clinicians should be aware that individuals with WITKOS may have a disharmonic intelligence profile, which can lead to misjudgment of their self-management capabilities. Many individuals with WITKOS will require some level of support throughout their lives.

Outcome and follow-up

Presently the child is in his early adolescence with mild intellectual disability and is able to perform all daily tasks. Follow-up includes ongoing endocrine evaluation for pubertal progression and growth monitoring. Neurodevelopmental support, educational planning, and psychosocial counselling are continued to optimize long-term functional outcomes and quality of life. Regular multidisciplinary follow-up remains essential.

DISCUSSION

In this case, we report the genetic diagnosis of heterozygous non sense pathogenic variant of SIN3A gene in a male child with clinical features of WITKOSSIN3A is part of a core histone deacetylase complex which is involved in transcriptional silencing mediated via interactions of repressors and corepressors. SIN3–HDAC–MECP2 corepressor complexes play an important role during various phases of embryonic development, such as cell cycle events and cell proliferation.[3] Interestingly, MECP2 has been suggested to participate in the epigenetic control of human pubertal timing.[10] In 2016, Witteveen et al demonstrated in animal models that SIN3A is expressed throughout the brain in developing mice, with higher concentrations in the subventricular zone, rostral migratory stream, and olfactory bulb. In vivo functional knockdown of SIN3A lead to reduced cortical neurogenesis, altered neuronal identity, and aberrant corticocortical projections. In humans, haploinsufficiency of SIN3A leads to a broad range of neurodevelopmental disorders, explained by reduced cortical neurogenesis.

Altogether, the evidence from patients with WITKOS and animal model studies has allowed to suggest that alterations in cortical expansion would be a direct consequence of SIN3A haploinsufficiency, leading to a broad range of neurodevelopmental disorders. A study by Meena Balasubramanian reported 56% patients to have global developmental delay while 44% had mild intellectual disability with an additional diagnosis of ADHD, aggressive behaviour, OCD, depression, psychosis, anxiety and schizoaffective disorder in a few patients. This is a significant finding, since such neuropathology has a significant impact on the quality of life of patients especially in those adults with milder neurodevelopmental phenotypes. Knowing that patients with variants in the SIN3A gene are at risk for such concerns, early intervention is important to ensure optimal treatment and outcomes. Varied expression of intellectual disability suggests that additional genes contribute to the cognitive phenotype in the 15q24 deletion syndrome.[3] Supporting the neurological manifestations, 46% patients were reported to have microcephaly. On imaging, findings of ventriculomegaly, hypoplastic or dysplastic corpus callosum and cerebellar atrophy were found in some of the patients with clinical manifestations like hypotonia and seizures.[5]

An impaired expression in the structures originating the olfactory bulb and GnRH neurons can explain the reproductive phenotype observed in our patient. The shortest region of overlap contains eight disease-related genes: COX5A, CYP11A1, EDC3, MAN2C1, MPI, SEMA7A, SIN3A, and STRA6. Of them, only SEMA7A plays a role in GnRH neuron migration in mice.[11] However, which of the eight deleted genes present in the shortest region of overlap is responsible for the reproductive phenotype in patients with WITKOS has not been determined. Cases of pubertal delay defined as the lack of occurrence of secondary sexual characteristics at an age that is at least two standard deviations later than the population mean, cryptorchidism, and micropenis, resulting from hypogonadotropic hypogonadism have been reported earlier in patients with WITKOS due to 15q24 microdeletions and another with a nonsense rare variant in the N-terminal region of SIN3A.[12,13,14,15] Another distinctive feature of WITKOS is craniofacial dysmorphism with common facial features including a broad, tall forehead, small mouth with a pointed chin and down-slanting palpebral fissures. Hyperlaxity of joints and short stature have also been reported in several cases. One study has shown that cardiac defects are not

uncommon findings in WITKOS patients, and they would benefit from early cardiac examination in terms of improved quality of life.[6] As observed in majority of the syndromic the neurologic symptoms and intellectual disability predominantly capture medical attention and drive patient management, interfering with a wider clinical assessment. WITKOS presenting with mild intellectual disability can often be missed in the early years. Cryptorchidism and micropenis can anticipate pubertal delay in male populations with hypogonadotropic hypogonadism, but may go undiagnosed if not specifically sought especially in the female population, given that there are no early clinical signs of hypogonadism prior to puberty.[16] In the present case, cryptorchidism with dysmorphic facies drove the genetic assessment in search for the etiology of hypogonadotropic hypogonadism.

An early etiologic diagnosis is important for the establishment of multidisciplinary management from an early age. For instance, therapy for neurodevelopmental delay; pharmacological treatment for psychiatric and behavioural problems needs to be initiated early. From the endocrinological standpoint, the surveillance of growth and pubertal onset impact the patient's quality of life deriving from social adjustment related to the acquisition of secondary sexual characteristics, adult height, and sexual maturity.

CONCLUSION

The need of early diagnosis and anticipation of subsequent manifestations of the syndrome during childhood along with a multidisciplinary approach to treatment has been emphasized.

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