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Case Report

Case report on Cabezas syndrome-where hypogonadism and obesity meet intellectual disability

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ABSTRACT

The symptom complex of obesity, hypogonadism and developmental delay are common to multiple syndromes. One such rare syndrome is the Cabezas syndrome caused by a wide spectrum of hemizygous variants in CUL4B gene, clinically characterized by myriad findings which include developmental delay/intellectual disability (ID), obesity, hypogonadism, typical and well recognizable somatic dysmorphisms, behavioural disturbances, ataxia and intention tremor. Worldwide, only a handful of cases of this syndrome have been reported in the last twenty-four years and our case is possibly the first reported case of Cabezas syndrome in India.

Keywords: Cabezas syndrome, CUL4B, Developmental delay, Hypogonadism, Obesity

INTRODUCTION

There's a vast spectrum of syndromic differentials for patients presenting with obesity, hypogonadism and developmental delay and reaching the diagnosis in such cases, solely on clinical grounds and radiological investigations, is not always possible. This is where genetic workup comes to our help.

Cabezas et al in the year 2000, studied by linkage and clinical examination, six affected males in three generations of a large family with peculiar symptom complex which included ID, short stature, obesity, small testes, muscle wasting, gait abnormalities and impaired speech.[1] A similar disorder was not found on review of the then XLMR (X-linked mental retardation) database of 124 syndromes and thus a novel XLMR syndrome localizing to Xq24-q25 was discovered. Tarpey and Zou led two independent groups in 2007 and identified mutations in CUL4B gene, a component of ubiquitin ligase complex, responsible for the disorder.[2,3] Until May 2022, 95 male individuals harbouring variants in CUL4B have been reported as per the literature review conducted by Vecchia et al.[5] The prevalence of CUL4B variations in X-linked ID is estimated to be between 2% and 3%.[2,5,6]

CASE REPORT

Our patient was a 14-month-old male toddler, second issue of a healthy non-consanguineous marriage, admitted with complaint of multiple episodes of generalized tonic-clonic seizures. There was no remarkable family history. He was a full term, vaginally-delivered appropriate for gestation neonate with no history of NICU (Neonatal Intensive Care Unit) stay. Antenatal history was not contributory. His 3-year-old sister was seemingly normal. Developmentally, he lagged behind in all four major domains, i.e., gross motor, fine motor, language and social. He could only sit with support, utter monosyllables, handle objects with bidextrous approach and immature pincer grasp. On examination, he was obese with high-arched palate, flat nasal bridge and plagiocephaly. He had spasticity in all limbs and deep tendon reflexes were brisk. Another significant finding was micropenis, with stretched penile length (SPL) of 2.1 cm (normal for age=4.2 cm).[8] Scrotal sac was empty. Ultrasonography (USG) for gonads revealed bilateral undescended small-sized testes with testicular volume of 0.3-0.4 CC (normal for age=2±0.4 cc). Magnetic resonance imaging (MRI) of brain reported open lip schizencephaly and absent septum pellucidum.

Optic nerve was normal. Thyroid function test and fundus examination were normal. Whole exome sequencing (WES) revealed hemizygous variant c.-2G>A (16×/16×) Exon 2 CUL4B gene (NM_003588.4) and genomic nomenclature chrX:g.119708474C>T with OMIM (Online Mendelian Inheritance in Man) phenotype-intellectual developmental disorder, X-linked syndromic, Cabezas type having X-linked recessive inheritance. An electroencephalogram was planned but could not be done owing to nonavailability of bedside facility.

Table 1: Anthropometry.

Parameters	Observed	Expected	Inference
Weight-for-age	14.2 kg	10 kg	>+3 SD
Length-for-age	80 cm	78 cm	Mean to +1 SD
Head circumference	47.5 cm	46.5 cm	Mean to +1 SD
Body mass index	22.19 kg/m^2	16.6 kg/m^2	>+3 SD
Weight-for-length	14.2 kg	10 kg	>+3 SD

Figure 1: Our case.

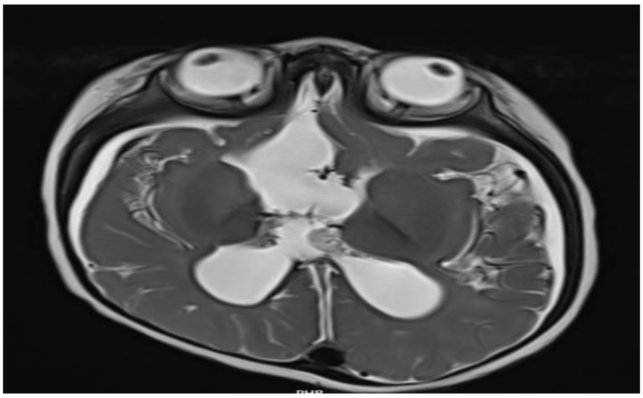

Figure 2: Open-lip schizencephaly.

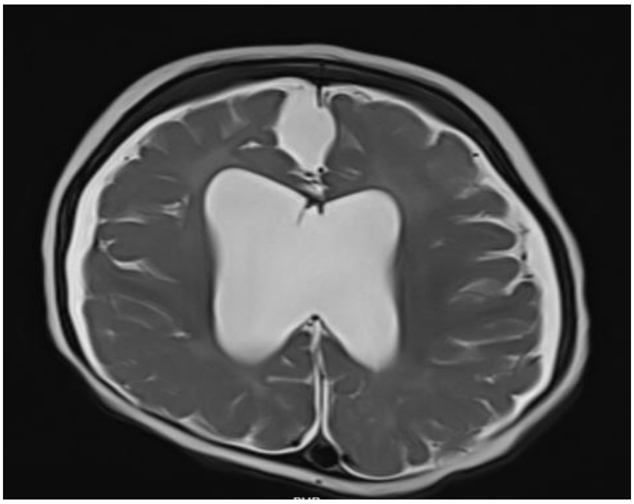

Figure 3: Absent septum pellucidum.

DISCUSSION

CUL4B is a relatively large gene with 913 amino acids, containing 21 coding exons (exons 2-22) that encode cullin-4b scaffold protein which forms the ubiquitin ligase complex (E3). It takes part in the process of ubiquitination of different substrates leading to alteration of protein function or degradation of proteins via 26S proteasomes.[9] CUL4B is known to be essential for normal neurological development.[6,10] Vulto-van Silfhout et al described variable and unspecific cerebral abnormalities in two-thirds of examined patients with CUL4B mutations.[6]

Cabezas syndrome (MIM 300354) is a recently identified syndromic form of XLMR caused by mutations in the CUL4B gene. The patients present with typical features such as obesity, hypogonadotrophic hypogonadism, developmental delay, somatic dysmorphisms (macrocephaly, short stature, coarse face, high forehead, prominent lower lip, malformed and/or abnormally positioned ears, small hands, brachydactyly), behavioural disturbances, ataxia and intention tremor. Nakamura et al compared the phenotypic features of previously-reported patients with CUL4B gene mutation aged <10 years and ≥10 years and found both groups had similar incidence of ID/motor and speech delay besides some form of somatic dysmorphism.[12] However, genital anomalies and obesity (17% each) were quite uncommon in patients <10 years as compared to those ≥10 years (82% and 63% respectively).

Brain MRI can show major and/or minor abnormalities (malformations of cortical development, ventriculomegaly, brain atrophy, cavum vergae, cavum septum pellucidum, thin corpus callosum and enlargement of the cisterna magna).[5]

Our patient was an obese male with hypogonadism, seizure disorder and developmental delay and contributory MRI and USG findings and an apparently normal sister. He presented symptomatically at a relatively younger age of 14 months, with obesity and genital abnormality manifesting earlier as compared to most other reported cases. He showed less marked phenotypic features compared with the previously-reported cases. In our patient, as in most reported cases, the diagnosis of Cabezas syndrome was established after the identification of pathogenic variants in CUL4B gene, suggesting that this syndrome is usually underdiagnosed. Parents were counselled regarding the nature of the illness and the risk of their future male offspring inheriting this disorder. They were advised genetic workup but this could not be done due to financial constraints.

Other differentials for the patient were Sengers-Hamel-Otten syndrome and MEHMO syndrome-both of which are X-linked genetic disorders. While such cases have previously been reported in various parts of the world, our case is possibly the first reported case of Cabezas syndrome in India.

CONCLUSION

CUL4B gene mutations should be considered in males with ID, speech and motor delay, obesity and behavioural abnormalities. The increasing use of next generation sequencing for undiagnosed ID cases has identified a number of pathogenic variants in patients with CUL4B-related ID and is helping us find a genetic explanation for rare or complex disorders. The clarification of the etiological diagnosis is necessary in order to answer the questions regarding the possibilities for therapeutic intervention and the risk of recurrence.

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REFERENCES

1. Cabezas DA, Slaugh R, Abidi F, Arena JF, Stevenson RE, Schwartz CE, Lubs HA. A new X linked mental retardation (XLMR) syndrome with short stature, small testes, muscle wasting, and tremor localises to Xq24-q25. J Med Genet. 2000;37(9):663-8.
2. Tarpey PS, Raymond FL, O'Meara S, Edkins S, Teague J, Butler A, et al. Mutations in CUL4B, which encodes a ubiquitin E3 ligase subunit, cause an X-linked mental retardation syndrome associated with aggressive outbursts, seizures, relative macrocephaly, central obesity, hypogonadism, pes cavus, and tremor. Am J Hum Genet. 2007;80(2):345-52.
3. Zou Y, Liu Q, Chen B, Zhang X, Guo C, Zhou H, et al. Mutation in CUL4B, which encodes a member of cullin-RING ubiquitin ligase complex, causes X-linked mental retardation. Am J Hum Genet. 2007;80(3):561-6.
4. Della Vecchia S, Lopergolo D, Trovato R, Pasquariello R, Ferrari AR, Bartolini E. CUL4B-associated epilepsy: Report of a novel truncating variant promoting drug-resistant seizures and systematic review of the literature. Seizure. 2023;104:32-37.
5. Vulto-van Silfhout AT, Nakagawa T, Bahi-Buisson N, Haas SA, Hu H, Bienek M, et al. Variants in CUL4B are associated with cerebral malformations. Hum Mutat. 2015;36(1):106-17.
6. López M, Pérez-Grijalba V, García-Cobaleda I, Domínguez-Garrido E. A 22.5 kb deletion in CUL4B causing Cabezas syndrome identified using CNV approach from WES data. Clin Case Rep. 2020;8(12):3184-8.
7. Jaiswal VK, Khadilkar V, Khadilkar A, Lohiya N. Stretched Penile Length and Testicular Size from Birth to 18 Years in Boys from Western Maharashtra. Indian J Endocrinol Metab. 2019;23(1):3-8.
8. Okamoto N, Watanabe M, Naruto T, Matsuda K, Kohmoto T, Saito M, et al. Genome-first approach diagnosed Cabezas syndrome via novel CUL4B mutation detection. Hum Genome Var. 2017;4:16045.
9. Kerzendorfer C, Hart L, Colnaghi R, Carpenter G, Alcantara D, Outwin E, et al. CUL4B-deficiency in humans: understanding the clinical consequences of impaired Cullin 4-RING E3 ubiquitin ligase function. Mech Ageing Dev. 2011;132(8-9):366-73.
10. Nakamura Y, Okuno Y, Muramatsu H, Kawai T, Satou K, Ieda D, et al. A novel CUL4B splice site variant in a young male exhibiting less pronounced feature. Hum Genome Var. 2019;6:43.

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