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Case Report

Prolonged jaundice evaluation opens a can of worms

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ABSTRACT

We present a case of a second-born male from a non-consanguineous marriage who exhibited prolonged jaundice. Upon clinical evaluation, he was found to have bilateral cryptorchidism and a micropenis. Further investigation revealed the presence of hypothyroidism. Due to the presence of abnormal genitalia and hypothyroidism, a comprehensive endocrine assessment was conducted, which identified deficiencies in multiple pituitary hormones. Genetic testing, prompted by persistent growth failure, confirmed a diagnosis of Culler-Jones syndrome (CJS) - a rare autosomal dominant disorder characterized by hypopituitarism, postaxial polydactyly and distinct facial abnormalities, including hypotelorism, cleft lip and palate, a flat nose and midfacial hypoplasia. This condition is caused by a heterozygous mutation in the GLI2 gene on chromosome 2q14.2. The phenotype of CJS is highly variable, demonstrating both incomplete penetrance and variable expressivity. In our case, the infant presented with combined pituitary hormone deficiency, an absent anterior pituitary gland, an ectopic posterior pituitary, significant growth retardation and underdeveloped genitalia. GLI2 mutations should be suspected in patients with congenital hypopituitarism, persistent growth failure (with or without abnormal facies) and polydactyly. Genetic testing is crucial for early diagnosis, as it facilitates better management, improves outcomes and helps anticipate the disease course.

Keywords: Culler-Jones syndrome, Hypopituitarism, Micropenis, Prolonged jaundice, Hypothyrodism

INTRODUCTION

Culler-Jones syndrome (CJS) is a rare autosomal dominant disorder caused by a mutation in the GLI2 gene on chromosome 2q14. It is characterized by hypopituitarism and/or polydactyly with abnormal facial features.[1]

The phenotype is highly variable, exhibiting incomplete penetrance and variable expressivity. Some patients present with development delay, cleft/lip palate, cryptorchidism, micropenis and short stature.[2] They are prone to epilepsy, psychomotor retardation and poor dentition.[3] Here, we present an infant with combined pituitary hormone deficiency, an absent anterior pituitary gland, an ectopic posterior pituitary, significant growth retardation and underdeveloped genitalia.

CASE REPORT

We report the case of a second-born male of a non-consanguineous marriage, born to an elderly mother with type 2 diabetes mellitus on insulin (HbA1c at conception 7.1%). The mother had a history of a stillbirth and an abortion. Her antenatal scans confirmed a diagnosis of Tetralogy of Fallot (TOF) in the fetus. Antenatal karyotype confirmed a 46 XY genotype. Since TOF was the only detectable anomaly, the pregnancy was continued. The baby was delivered via Caesarean section at 37+4 weeks of gestation.

At birth, he weighed 2.84 kg. Clinical examination revealed bilateral cryptorchidism and a micropenis (Figure 1a). He experienced a few episodes of hypoglycaemia, which were appropriately managed. At 21 days of life, he presented with prolonged jaundice and

upon evaluation, was diagnosed with hypothyroidism. Due to the combination of cryptorchidism, micropenis and hypothyroidism, a detailed endocrine evaluation was performed, revealing multiple pituitary hormone deficiencies. Hypothyroidism: Thyroid Stimulating Hormone (TSH)- 6.40 IU/ml. Secondary adrenal insufficiency: Cortisol-2.2 mcg/dl. Growth hormone deficiency: insulin-like growth factor-1 (IGF-1)-19 ng/ml. Hypogonadotropic hypogonadism: Luteinizing Hormone (LH)<0.1 IU/l, Follicle-stimulating Hormone (FSH)-0.46 IU/l and testosterone<2.5 ng/dl. MRI brain showed an absent anterior pituitary gland and stalk with an ectopic posterior pituitary (Figure 1b).

Due to ACTH, TSH, GH, LH and FSH deficiencies, he was started on hydrocortisone (12 mcg/m^2/day), levothyroxine (11.2 mcg/kg/day) and human menopausal gonadotropin (HMG) 75IU, thrice weekly, for hypogonadotropic hypogonadism. There was a poor clinical and biochemical response to HMG at 4 months of age, prompting the parents to continue treatment with recombinant testosterone. At 1 year and 4 months of age, he received three intramuscular doses of testosterone (25 mg each), which resulted in minimal improvement in genital development.

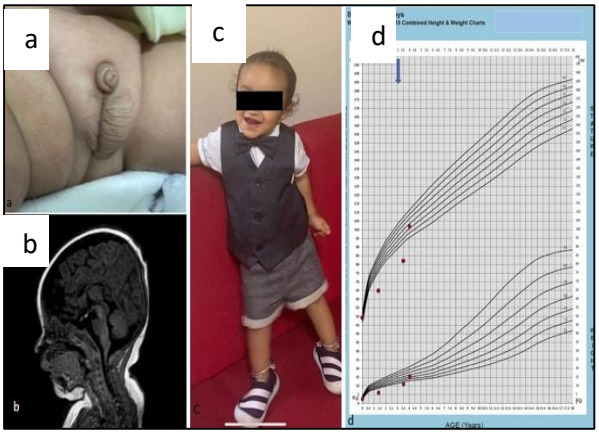

Figure 1: (a) Illustrates micropenis accompanied by cryptorchidism. (b) Displays the MRI brain, revealing an absent anterior pituitary gland and an ectopic posterior pituitary. (c) Shows significant growth faltering, evident when the picture was taken at the age of three years. (d) Presents a growth chart highlighting noticeable growth retardation; height is more adversely affected than weight, suggesting an endocrine cause. The blue arrow indicates the initiation of GH therapy. Growth improved following the supplementation of GH.

The child continued to fail to thrive despite optimized hydrocortisone and levothyroxine therapy. TOF was surgically corrected at 12 months of age and at 1.5 years, he underwent a right inguinal herniotomy and orchidopexy for a hernia that developed during infancy. In light of persistent growth failure, clinical exome sequencing was performed, revealing a heterozygous mutation in exon 10 of the GLI 2 gene, confirming a diagnosis of Culler- Jones Syndrome (CJS).

At 16 months, his weight was 6.8kg and his height was 65cm (-3 SD on Indian growth charts), indicating significant growth retardation. He was started on growth hormone injections at 3 years (Figure 1c). At 4 years, his weight was 16.2 Kg and his height was 102 cm (50th percentile), indicating a good response to therapy (Figure1d).

DISCUSSION

CJS is an autosomal dominant disorder characterized by hypopituitarism, postaxial polydactyl and distinctive facial abnormalities, including hypotelorism, cleft lip/palate, a flat nose and midfacial hypoplasia. It results from a heterozygous GLI2 gene mutation on chromosome 2q14.2.[4] The phenotypic presentation is highly variable, exhibiting incomplete penetrance and variable expressivity. In our case, the patient presented with combined pituitary hormone deficiency, an absent anterior pituitary, an ectopic posterior pituitary, severe growth retardation and poor genital development.

GLI2 plays a critical role in embryonic development by regulating gene expression and repression. It is a transcription factor involved in Sonic Hedgehog signaling, which is essential for Rathke's pouch development and pituitary progenitor proliferation.[5] Among the four known human GLI genes, mutations in GLI2 and GLI3 lead to distinct syndromes. GLI3 is particularly crucial for finger development, while GLI2A (an activator form of GLI2) significantly affects pituitary and midface development.[6,7]

Although cardiac malformations are not commonly associated with CJS, other congenital heart defects (such as ASD, VSD and PDA) have been reported with various GLI mutations. Given that GLI2 is known to play a role in cardio myogenesis, this may explain the TOF in our patient.[8] Additionally, maternal pregestational diabetes is known to modestly increase the risk of TOF and other conotruncal anomalies.[9]

CONCLUSION

Neonatal hypoglycemia with abnormal genitalia should prompt an endocrine evaluation. GLI2 mutations should be suspected in patients with congenital hypopituitarism, persistent growth failure, polydactyly and/or abnormal facial features. Genetic testing is crucial for early diagnosis, optimized management and better clinical outcomes, allowing for early intervention and anticipation of disease progression.

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REFERENCES

1. Demiral M, Demirbilek H, Unal E, Durmaz CD, Ceylaner S, Özbek MN. Ectopic Posterior Pituitary, Polydactyly, Midfacial Hypoplasia and Multiple Pituitary Hormone Deficiency due to a Novel Heterozygous IVS11-2A>C(c.1957-2A>C) Mutation in the GLI2 Gene. J Clin Res Pediatr Endocrinol. 2020;12(3):319–28.
2. Niida Y, Inoue M, Ozaki M, Takase E. Human Malformation Syndromes of Defective GLI: Opposite Phenotypes of 2q14.2 (GLI2) and 7p14.2 (GLI3) Microdeletions and a GLIA/R Balance Model. Cytogenet Genome Res. 2017;153(2):56–65.
3. Bragança R, Pimenta S, Brandão C, Machado L, Barbosa R. Culler-Jones Syndrome. Int J Med Rev Case Rep. 2021;5(4):33–5.
4. Bear KA, Solomon BD, Antonini S, Arnhold IJP, França MM, Gerkes EH, et al. Pathogenic mutations in GLI2 cause a specific phenotype that is distinct from holoprosencephaly. J Med Genet. 2014;51(6):413–8.
5. Roessler E, Du YZ, Mullor JL, Casas E, Allen WP, Gillessen-Kaesbach G, et al. Loss-of-function mutations in the human GLI2 gene are associated with pituitary anomalies and holoprosencephaly-like features. Proc Natl Acad Sci. 2003;100(23):13424–9.
6. Al-Qattan MM, Shamseldin HE, Salih MA, Alkuraya FS. GLI3-related polydactyly: a review. Clin Genet. 2017;92(5):457–66.
7. Gregory L, Gaston-Massuet C, Andoniadou C, Carreno G, Webb E, Kelberman D, et al. The role of the sonic hedgehog signalling pathway in patients with midline defects and congenital hypopituitarism. Clin Endocrinol (Oxf). 2015;82(5):728–38.
8. Fair JV, Voronova A, Bosiljcic N, Rajgara R, Blais A, Skerjanc IS. BRG1 interacts with GLI2 and binds Mef2c gene in a hedgehog signalling dependent manner during in vitro cardiomyogenesis. BMC Dev Biol. 2016;16(1):27.
9. Pre-pregnancy diabetes and offspring risk of congenital heart disease. circulation. Available at: https://www.ahajournals.org. Accessed on 21 November 2024.

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