Mutations in ZBTB20 cause Primrose syndrome in a Pediatric Patient: A Case Report

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Abstract

Background: Macrocephaly, hypotonia, developmental delay, intellectual disability with delayed expressive speech, behavioral issues, a distinct facial phenotype, radiographic abnormalities, and impaired glucose metabolism are characteristics of the Primrose syndrome. As a result, Primrose syndrome is identified in a proband with typical symptoms and a heterozygous pathogenic mutation in ZBTB20 identified by molecular genetic testing.

Case presentation: A seven-year-old girl presented with a history of not speaking consistently, snoring and mouth breathing. The patient was responding to sound and there was presence of adenoid hypertrophy. Four years later, the patient presented with developmental delay, delayed speech and problem sleeping. Whole exome sequencing (WES) was done and the result showed a likely heterozygous pathogenic variant, c.11+1del, in the ZBTB20 gene. As advised, management includes educational programs, physiotherapy, speech therapy, and occupational therapy.

Conclusion: Patients must have their growth and development followed every six months, their speech and developmental needs evaluated every six months, their behavioural issues, neurological, and musculoskeletal conditions evaluated at every visit, their brain stem evoked response audiometry evaluated annually, and their thyroid function and insulin-resistant diabetes tested annually.

Keywords: Heterozygous, Mutation, ZBTB20, Primrose, syndrome, Jeddah

Introduction

The diagnosis of Primrose syndrome is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in ZBTB20 identified by molecular genetic testing, like sequence analysis 4 or gene targeted deletion /duplication analysis (1).

Depending on the phenotype, molecular genetic testing methods include a combination of targeted gene testing (single-gene testing, multigene panels) and comprehensive genomic testing (exome sequencing, genome sequencing) (2).

If phenotype, laboratory, and imaging findings suggest a diagnosis of primrose syndrome, molecular genetic testing may include use of single-gene testing or multigene panels: single genetic testing. First, we perform sequence analysis of ZBTB20 to detect small intragenic deletions/insertions, as well as missense, nonsense, and splice site variants (1,3).

Depending on the sequencing technique used, single-exon, multi-exon, or whole-gene deletions/duplications may not be found. The next step is to perform gene-specific deletion/duplication analysis to find exonic and whole-gene deletions or duplications if no variants are found by the sequencing technology used (4).

The best way to discover the underlying genetic etiology of the problem and limit its impact is to use a multigene intellectual disability panel that includes ZBTB20 and other genes of interest (see Differential Diagnosis) (5).

Comprehensive genomic testing of ZBTB20 is an option when the phenotype is difficult to distinguish from various other genetic disorders characterized by developmental delay or macrocephaly. The most common type of sequencing is exome sequencing, but genomic sequencing is also possible (6).

Case presentation

A seven-year-old girl who was initially seen at the age of 3 years and 7 months, presented with a history of not speaking consistently, snoring and mouth breathing. Upon examination, the patient was responding to sound and there was presence of adenoid hypertrophy. Four years later, the patient presented with developmental delay, delayed speech and problem sleeping. A pediatric evaluation revealed unusual behaviors such as hand flapping and arms lifting while walking but no apparent facial abnormality. We ordered Whole Exome Sequencing (WES) and a likely heterozygous pathogenic variant, c.11+1del, in the ZBTB20 gene was detected. Defects in the ZBTB20 gene cause disorder(s) include Primrose syndrome. Education programs, physiotherapy, speech therapy, and occupational therapy are all included in the management, as recommended.

Discussion

Primrose syndrome is a rare syndrome, usually unrecognized in childhood. Patients display a specific association in late childhood or adulthood, with distinctive features, such as hearing loss, pinnae calcification, endocrine manifestations and muscle wasting (7).

Primrose syndrome can present as an overgrowth syndrome with respect to brain growth, however increase in height and weight is less marked and present in a minority of patients. Some females grow below the third centile for height and weight (8).

The cardinal findings of PS include intellectual disability, mildly increased growth, and the most characteristic signs are calcified external ears, sparse body hair, bone dysplasia and distal muscle wasting (9).

The calcification of the ears, cataract, torus palatinus, cystic bone lesions and muscle wasting with subsequently contracture formation are age-related and become apparent in puberty. Cognition does not seem to decline with age. Hearing loss is common, mostly presenting as sensorineural hearing loss (8).

The progression in signs and symptoms with age may point to a metabolic disturbance. Unexplained anemia, disturbed glucose metabolism, and increased AFP levels are the main features of primrose syndrome (8, 10).
Further metabolic investigations revealed abnormal acylcarnitine and urine organic acid profiles in some patients, including increased excretion of dicarboxylic acids, ethylmalonic and glutaric acids (11).

Conclusion

Primrose syndrome is a rare condition caused by ZBTB20 gene mutation, characterized by facial features, macrocephaly with intellectual disability, developmental delay and abnormal glucose metabolism. It is diagnosed by molecular genetic testing. Management includes educational program, speech therapy, physical therapy, and occupational therapy. Patients require monitoring growth and development every six months, speech and developmental assessment every six months, assessment for behavioral issues, neurological and musculoskeletal complications at each visit, annual brain stem evoked response audiometry and annual screening for insulin-resistant diabetes and thyroid dysfunction.

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Authors' contribution
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Conflicts of interest
The authors declare that there are no conflicts of interests.

Data and materials availability
All data associated with this study are present in the paper

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