A Novel Association of Campomelic Dysplasia with Hydrocephalus Due to an Unbalanced Chromosomal Translocation Upstream of SOX9

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Introduction

Campomelic dysplasia is a rare skeletal dysplasia characterized by Pierre-Robin sequence, craniofacial dysmorphism, shortening and angulation of long bones, tracheobronchomalacia, and occasionally sex reversal. The disease is due to mutations in SOX9 or chromosomal rearrangements involving the long arm of chromosome 17. Intracranial abnormalities, including ventriculomegaly, which has only been reported once before, are poorly understood and management is unclear.

Methods

The clinical chart was reviewed for the index patient. Comparative genomic hybridization (CGH) and whole exome sequencing (WES) were performed in blood-derived DNA.

Results

The patient was diagnosed with campomelic dysplasia at birth, demonstrating angulation and shortening of long bones and external female genitalia on prenatal ultrasound and found to have 46, XY, t(6;17) (p21.1;q24.3) on prenatal genetic testing. At birth, no intracranial abnormalities were noted on surveillance imaging. At two-months, she presented with lethargy and acute respiratory distress requiring intubation. Head ultrasound and subsequent brain MRI demonstrated new ventriculomegaly with globally dilated ventricles but patent flow around the foramen magnum. Clinically, she showed no signs of increased ICP over the following two months and was managed expectantly with serial examination and imaging. Further testing via CGH revealed deletions at 6p21.1 and 17q24.3, the latter being 2.3Mb upstream of SOX9. WES did not identify pathogenic variants in SOX9, suggesting that the 17q24.3 deletion may affect expressivity of SOX9 and may represent a cluster of translocation breakpoints farther upstream of SOX9 than previously described.

Conclusions

The case demonstrates acquired ventriculomegaly as a novel presentation of campomelic dysplasia that may be secondary to an ex vacuo phenomenon related to neural migration defects from SOX9 dysfunction and thus not neurosurgical intervention. It also demonstrates a novel chromosomal breakpoint and suggests a new cluster of noncoding loci that control expression of SOX9, which may preferentially affect neuronal development.

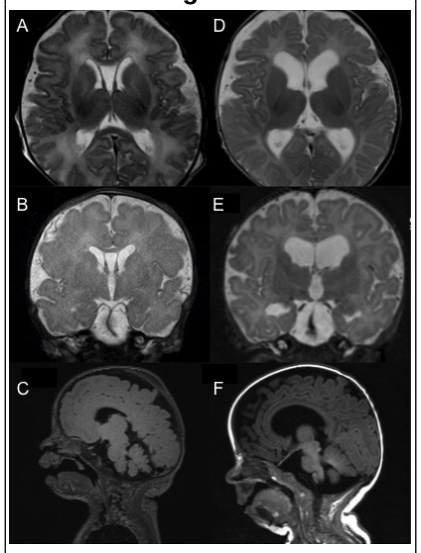
Learning Objectives

1. Recognize ventriculomegaly is a rare but potential neurological manifestation of campomelic dysplasia.
2. Understand that the ventriculomegaly in campomelic dysplasia may be secondary to an ex vacuo phenomenon with normal ICPs and thus not require neurosurgical intervention.
3. Recognize chromosomal deletions at 17q24.3 as novel pathogenic translocation breakpoints far upstream of SOX9 in campomelic dysplasia, which may preferentially affect neuronal development.

References

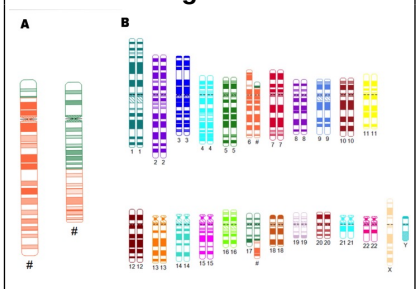
Matsumoto A, Imagawa E, Miyake N, et al. The presence of diminished white matter and corpus callosal thinning in a case with a SOX9 mutation. Brain Dev. Apr 2018;40(4):325-329.

Figure 1



Acquired diffuse ventriculomegaly as a manifestation of campomelic dysplasia. At birth the patient had no radiographic evidence of ventriculomegaly on (A) axial T2-weighted (B) coronal T2-weighted and (C) sagittal T2-weighted FLAIR MR images. At two-months, there was interval development of global ventriculomegaly with dilation of the lateral, third, and fourth ventricles but no clinical evidence of increased intracranial pressure, as seen on (D axial T2-weighted (E) coronal T2-weighted and (F) sagittal T2-weighted FLAIR MR images.

Figure 2



(A) Ideogram and (B) karyogram demonstrating the unbalanced translocation in the index patient.