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(Citation)
Pediatrics International,62(1):115-117

(Issue Date)
2020-01

(Resource Type)
journal article

(Version)
Accepted Manuscript

[Clinical Notes]

MPPH syndrome with aortic coarctation and macrosomia due to *CCND2* mutations

Running title: MPPH syndrome with aortic coarctation

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Number of text pages; 5

Number of words; 783

Reference pages; 1

Tables; 0 (Supplemental Table 1)

Figures and legends to figures; 1

Key words

aortic coarctation, *CCND2*, hydrocephalus, MPPH syndrome, postaxial polydactyly

Megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH) syndrome is a rare autosomal dominant disorder, characterized by progressive megalencephaly, polymicrogyria, and postaxial polydactyly.[1] Patients with this syndrome have a high risk of developing hydrocephalus, mild to severe intellectual disabilities, and epilepsy.[1] The clinical symptoms of megalencephaly-capillary malformation (MCAP) syndrome overlap with those of MPPH syndrome.[2] Genetic mutations in phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT) pathway components cause both MPPH and MCAP syndromes; *AKT3*, *PIK3R2*, and *CCND2* are associated with MPPH syndrome,[1] whereas *PIK3CA* somatic mosaicism mutations are associated with MCAP syndrome. The primary difference between these two syndromes is the presence of hemihypertrophy and somatic vascular malformations in MCAP syndrome.

A Japanese boy who presented with ventricular enlargement at 28-weeks gestational age was born at gestational age 38 weeks and 2 days. His birth weight was 4,102 g (+3.79 SD), height was 52.2 cm (+2.16 SD), and head circumference was 38.8 cm (+4.44 SD). His Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. He also presented with forehead protrusion, sacral cusp depression, low auricle, depressed nasal bridge and postaxial polydactyly, but no somatic asymmetry. Echocardiography revealed aortic coarctation (Fig. 1a), and no other cardiac malformations were observed.

The head magnetic resonance imaging performed at the age of 4 days confirmed ventricular enlargement and polymicrogyria (Fig. 1b). At the age of 6 months, the patient had a height of 74.4 cm (+2.8 SD), a weight of 11.3 kg (+3.7 SD), and a head circumference of 49.5 cm (+5.6 SD). He was diagnosed with epilepsy at the age of 1 year, 3 months and started valproate and clobazam. At the age of 1 year, 9 months, he remained unable to hold up his neck but could roll over his trunk. At the age of 2 years, his weight was 11.7 kg (+0.16 SD), his height was 88.0 cm (+0.85 SD) and head circumference of 54.8 cm (+4.1 SD). His karyotype was 46,XY.

We clinically diagnosed him as MPPH syndrome or MCAP syndrome. To confirm the molecular diagnosis, we performed a genetic analysis of the patient at the age of 1 month, after obtaining written informed consent from his parents. All procedures were reviewed and approved by the Institutional Review Board of Kobe University School of Medicine. DNA was extracted from peripheral blood mononuclear cells. We first performed next-generation sequencing, using the TruSight One Sequencing (TS1) Panel (Illumina, San Diego, CA, USA), which can analyze 4,813 genes, including *AKT3*, *PIK3R2*, and *PIK3CA*. However, we were unable to identify his causative gene using TS1. Next, we analyzed *CCND2,* at the age of 2 months, using Sanger sequencing, and found a heterozygous missense variant in *CCND2*,

NM_001759.3:c.842C>G, p.Pro281Arg (Fig. 1c), which is a known disease-causing mutation (HGMD CM144536, ClinVar RCV000133499.3). The in-silico analyses also indicated the mutation to be pathogenic (CADD score; 30, SIFT; deleterious, PolyPhen2; probably damaging, Mutation Taster; disease causing and PROVEAN; deleterious), as evaluated by wANNOVAR.[3] We did not perform a segregation analysis on his parents.

The PI3K-AKT pathway is one of the most important intracellular signaling pathways, associated with cellular proliferation and cancer formation. Germline or somatic mutations in genes associated with this pathway have been reported to cause several overgrowth syndromes, including Proteus syndrome (*AKT1*), Cowden syndrome, and CLOVES syndrome (*PIK3CA*). Our patient had megalencephaly, which can indicate either MPPH or MCAP syndrome, and these syndromes have some overlapping phenotypes (Supplemental Table 1). We were unable to identify any pathogenic variants in the TS1 panel, which includes *AKT3*, *PI3R2*, and *PIK3CA*, but were able to identify the responsible mutation in *CCND2* by additional Sanger sequencing.

Clinical phenotypical differences in MPPH syndrome among three gene mutations have been reported. MPPH syndrome associated with an *AKT3* mutation may

show connective tissue laxity and cutaneous capillary malformations.[1] Hypoglycemia was reported in patients with overgrowth syndromes, especially those with *PIK3CA* or *CCND2* mutations.[4] However, our patient showed no glucose abnormalities. Patients with MPPH syndrome caused by *CCND2* mutation tend to present more severe clinical manifestations, including intellectual disabilities and polymicrogyria.[1] Congenital cardiovascular defects, such as ventricular or atrial septal defects, have been observed in some patients with MPPH syndrome,[1] but no reports regarding patients with MPPH syndrome caused by *CCND2* mutations who present with aortic coarctation exist. MPPH syndrome caused by *CCND2* mutations is extremely rare; therefore, further investigation and the identification of more patients is necessary to better understand MPPH syndrome.

In conclusion, we were able to successfully and rapidly diagnose MPPH syndrome using a comprehensive genetic analysis and clinical diagnosis. Aortic coarctation can be viewed as a new phenotype for MPPH syndrome.

Acknowledgments

The authors thank the patient and his family. We thank Lisa Giles, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Disclosures

KI received grants from Daiichi Sankyo Co. Ltd., Zenyaku Kogyo Co., Ltd. and Astellas Pharma. The other authors declare no conflict of interest.

Author contributions

T.S. designed the study and wrote the manuscript. T.E. and M.K. evaluated the patient and collected and interpreted the data. N.M. performed the genetic analysis and genetic counselling for the family. K.I. evaluated the patient, discussed the results, and gave final approval. All authors read and approved the final manuscript.

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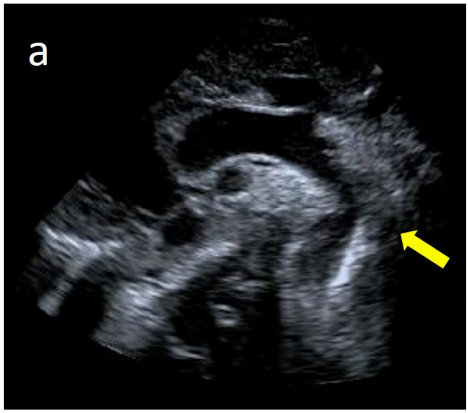
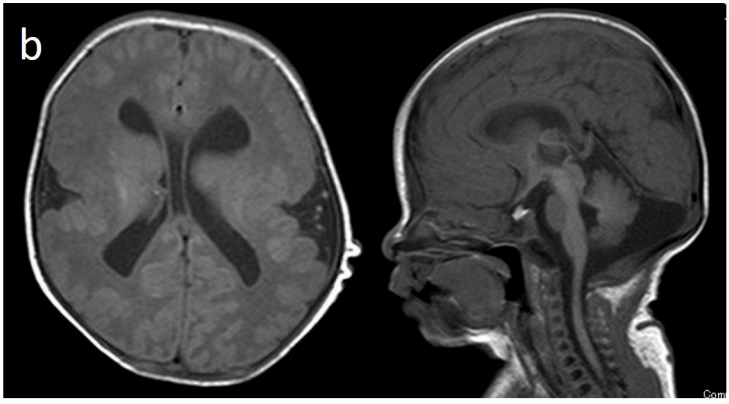
Figure Legend

Fig. 1 Echocardiogram at the age of 2 days. The coarctation is indicated by a yellow arrow (30 mm) (a). Brain magnetic resonance imaging of the patient at the age of 4 days (b). Bilateral enlargement of the ventricle and polymicrogyria can be observed. Sanger sequencing of *CCND2* for the patient (c).





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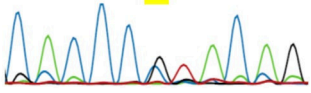

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