BRIEF COMMUNICATION

Type B Interrupted Aortic Arch and Hydrocephalus Associated with Mosaicism of a 1.37 Mb Amplified Cat Eye Syndrome Critical Region

Meng-Che Tsai a, Yen-Yin Chou a,⁎, Jieh-Neng Wang a, Jing-Ming Wu a, Chao-Ching Huang a,b, Pao-Lin Kuo c, Yi-Shan Tsai d

a Department of Pediatrics, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
b Department of Pediatrics, College of Medicine, Taipei Medical University, Taipei, Taiwan
c Department of Obstetrics and Gynecology, National Cheng Kung University Hospital, College of Medicine, National Cheng-Kung University, Tainan, Taiwan
d Department of Diagnostic Radiology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Received Jul 9, 2014; received in revised form Sep 12, 2014; accepted Oct 10, 2014
Available online 3 January 2015

1. Introduction

Cat eye syndrome (CES) is a rare chromosomal disorder with a variable complex of clinical presentations, ranging from nearly normal to severely debilitated patients. The characteristic features consist of ocular coloboma, craniofacial dysmorphism, preauricular pits or tags, anorectal anomalies, cardiac and renal malformations, and occasional developmental retardation. ¹ The diagnosis is usually made based on the presence of a small supernumerary marker chromosome (sSMC) derived from chromosome 22. ² Technological advancements have narrowed down the CES critical region to the proximal segment of 22q11. ² Changes with either an increased or a decreased gene dosage within this region have been implicated in the common clinical phenotypes shared by DiGeorge/velocardiofacial syndrome (DGS/VCFS), microduplication 22q11.2 syndrome, and also some cases of CES. ³ However, the typical phenotypic features differ in frequency among these disorders, given that the chromosomal region involved in CES is different from and lies proximally to that of DGS/VCFS. Herein, we reported a patient with mosaicism for a sSMC 22 presenting multiple cardiac, neurological, and skeletal anomalies in the absence of ocular coloboma.

2. Patient data

The patient was born to Taiwanese parents with an uneventful antenatal history. After birth, the physical examination revealed macrocephaly with a head circumference of 39 cm (>97th percentile), bilateral preauricular pits, preaxial polydactyly on the right hand, and bilateral...
inguinal hernias (Figure 1A–C). Cardiopulmonary evaluation showed an infrahyoid branchial cyst on the left side and complex cardiac anomalies, including the presence of a type B interrupted aortic arch (IAA), patent ductus arteriosus, and a subaortic ventricular septal defect (Figure 1D). Consequently, he received surgical reconstruction of the aortic arch, repair of the septal defect, and removal of the neck cyst. Furthermore, cerebral echography initially found bilateral subependymal cysts. These cerebral lesions progressed in size, and brain magnetic resonance imaging showed marked dilation of the bilateral lateral ventricles, the third ventricle, and the prepontine cistern (Figure 1E). Obstruction brought by the progressing cyst was evident at the level of cerebropontine junction. Neurosurgical decompression was conducted by ventriculostomy of the third ventricle and ventriculoperitoneal shunting. Detailed ophthalmological examination did not reveal any coloboma of the ocular structures in the follow-up. The patient was more remarkably delayed in gross motor skills as compared to social and language skills at 14 months of age.

The conventional chromosomal study on cultured lymphocytes showed a mosaic composition of G-banded metaphase cells with an sSMC present in approximately 50% of the analyzed cells (Figure S1). This bisatellited and pseudosodicentric sSMC was conceived to arise de novo, because there were no numerical or structural aberrations in the patient’s

Figure 1  Patient shows (A) macrocephaly, (B) bilateral preauricular pits, and (C) preaxial polydactyly without ocular coloboma at 3 months of age. (D) The ECG-triggered cardiac CT angiography with a three-dimensional image using a volume-rendering technique reveals a type B interruption of the aortic arch and the blood flow of the descending aorta via patent ductus arteriosus, while (E) the sagittal brain MR image using fast imaging and employing steady-state acquisition depicts nonobstructive hydrocephalus and a prepontine cyst posing a mass effect on pituitary stalk and the floor of the third ventricle. CGH = comparative genomic hybridization; CT = computed tomography; ECG = electrocardiogram; MR = magnetic resonance.
parental karyotypes. Commercially available array comparative genome hybridization chips (CytoChip Oligo; BlueGene, Cambridge, UK) were applied to delineate the characteristics of the \textit{de novo} marker chromosome. The chip contained approximately 60,000 probes at a resolution of 60 kb. Array analysis showed a duplication of 1.37 Mb spanning from genomic position 15,777,528 to 17,145,109 at chromosome 22q11. This segment contained genes within CES critical region, including IGKV2OR22-3, IGKV3OR22-2, IGKV1OR22-1, GAB4, IL17RA, CECP6, CECR5, CECR1, FAM32B, CECR2, SLC25A18, ATP6V1E1, BCL2L13, BID, MICAL3, MIRN648, PEX26, TUBA8, USP18, and GGT3P, without extension to the DGS/VCFS region (Figure S2). Overall, the genotype was given as 47,XY, +mar(22) dn[10]/46,XY[10]. arr 22q11.1q11.21(15,777,528–17,145,109) \times 3, confirming the diagnosis of CES.

3. Discussion

In summary, our findings highlight the phenotypic variability of CES. IAA and intracranial cysts are rare, but can exist in CES cases without other cardinal features. Despite the link between cardiac anomalies and CES, only one case with IAA was previously reported, which stands in great contrast to frequent occurrences associated with microdeletion or microduplication of 22q11.2. Our case echoed this finding by showing the breakpoint located in the distal end of GGT3P, outside of DGS/VCFS region. Although the CECR1 is conceived in association with cardiac anomalies in CES patients, IAA remains a rare manifestation. Marked variability in expressivity or penetrance can be expected in these patients, and may be explained by the existent genomic mosaicism usually shown in sSMC.

Polydactyly is another feature frequently associated with DGS/VCFS. It is rare but was recently reported in one CES patient. The \textit{TBX1} gene encoding an important transcriptional factor implicated in numerous developmental processes and contained in the DGS/VCFS region has been tentatively correlated with the occurrence of polydactyly. However, the supernumerary marker in our patient did not include \textit{TBX1}. A few research results have suggested an important role of other unknown genes or complex interactions between amplified regions in the pathogenesis.

Neurodevelopmental outcomes have been wide ranging; however, anatomic pathology of the central nervous system has rarely been delineated in CES. Candidate genes contained in the duplicated segment may include \textit{MICAL3} (cytoplasmic effector to trigger neuronal reorganization) and \textit{TUBA8} (cytoskeletal protein involved in neuronal migration). Karcaaltincaba et al reported a Turkish fetus with \textit{de novo} duplication of chromosomal 22q11.1–22q11.3, presenting an interhemispheric cyst and corpus callosum agenesis. Meanwhile, Romagna et al reported an adolescent Brazilian girl who was incidentally found to have enlarged ventricles and a marker chromosome 22 during the investigation of the cause of her developmental delay. In our patient, with prompt surgical management, further severe neurodevelopmental impairment potentially caused by progressive hydrocephalus was prevented. Given the possibility of neurological involvement in CES, we propose that patients with neurological deficits should be meticulously investigated for any explainable anatomic lesions.

Conflicts of interest

We have no conflicts of interest to declare.

Acknowledgments

We appreciate the technical support for array comparative genome hybridization provided by the Sofiva Genomics Laboratory of Dianthus Maternal Fetal Medicine Clinic (Taipei, Taiwan), directed by Dr Yi-Ning Su.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pedneo.2014.10.009.

References