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Persistent Trigeminal Subtype of Internal Carotid Artery Agenesis in CHARGE Syndrome

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Dear Editor,

CHARGE syndrome (OMIM 214800) is a disease with multiple congenital anomalies. Loss-of-function pathogenic variants of the *CHD7* (chromodomain helicase DNA-binding protein) gene are found in a large proportion of patients,[1] and approximately 70% of patients with CHARGE syndrome present with pathogenic variants of this gene. The prevalence of CHARGE syndrome is approximately 1 in 10,000 births, with similar incidence rates in males and females. Patients with CHARGE syndrome may show various clinical features, including severe intellectual disability, external ear anomaly, semicircular canal anomaly, coloboma, cleft lip and/or palate, cranial nerve dysfunction, feeding difficulties, and congenital heart defects. The phenotypic spectrum and pathogenic mechanisms of CHARGE syndrome remain unclear, and early treatment of symptoms is important for the prognosis.[2] Congenital heart defects are major anomalies in patients with CHARGE syndrome, but their relationship with the cerebral vascular anomaly remains unresolved.[3-5] Internal carotid artery (ICA) agenesis is a very rare cerebral anomaly, and it has various subtypes that result in neurological symptoms such as headache, pulsatile tinnitus, ischemic stroke/transient ischemic attack, and Horner's syndrome.[6] The persistent trigeminal subtype of ICA agenesis is particularly rare.[6-9] Here we present a case of the persistent trigeminal subtype of left ICA agenesis in a 17-year-old male patient with CHARGE syndrome.

The patient presented with headache and irritability. He had multiple anomalies, including global developmental delay, atrial septal defect, patent ductus arteriosus, hearing impairment, left cone-shaped auricle, facial palsy, right complete cleft palate, esophageal hiatal hernia, hypothyroidism, micrognathia, hiatal hernia, and feeding difficulty. Genetic testing using whole-exome sequencing revealed the heterozygous pathogenic variant c.6079C>T (p. Arg2027Ter) in *CHD7* (NM_017780.4). The patient underwent gastrostomy and fundoplication when he was 5 months old and palatoplasty when he was 12 years old. Upon admission, he underwent brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) due to the recent recurrent headache and irritability. No specific findings other than mild plagiocephaly were found in brain MRI, whereas MRA revealed the cerebral vascular anomaly of left ICA agenesis and left persistent trigeminal artery, which was directly connected from the basilar artery to the left middle cerebral artery (Fig. 1).

Congenital absence of the ICA is known to be asymptomatic in most cases, but rare reports exist of its association with the anomalies of corpus callosum agenesis, neurofibromatosis, meningocele, coarctation, and cardiac anomalies. Surgical treatment is not required in asymptomatic cases, but the high prevalence of cerebral aneurysms associated with ICA agenesis makes periodic brain MRA follow-up necessary. In addition, cyproheptadine is known to be effective in cases of migraine-like attacks, which were present in our patient.[4,6]

The trigeminal artery is one of the fetal arterial circulations connecting the anterior and posterior cerebral circulations. The reported incidence of persistent trigeminal artery ranges

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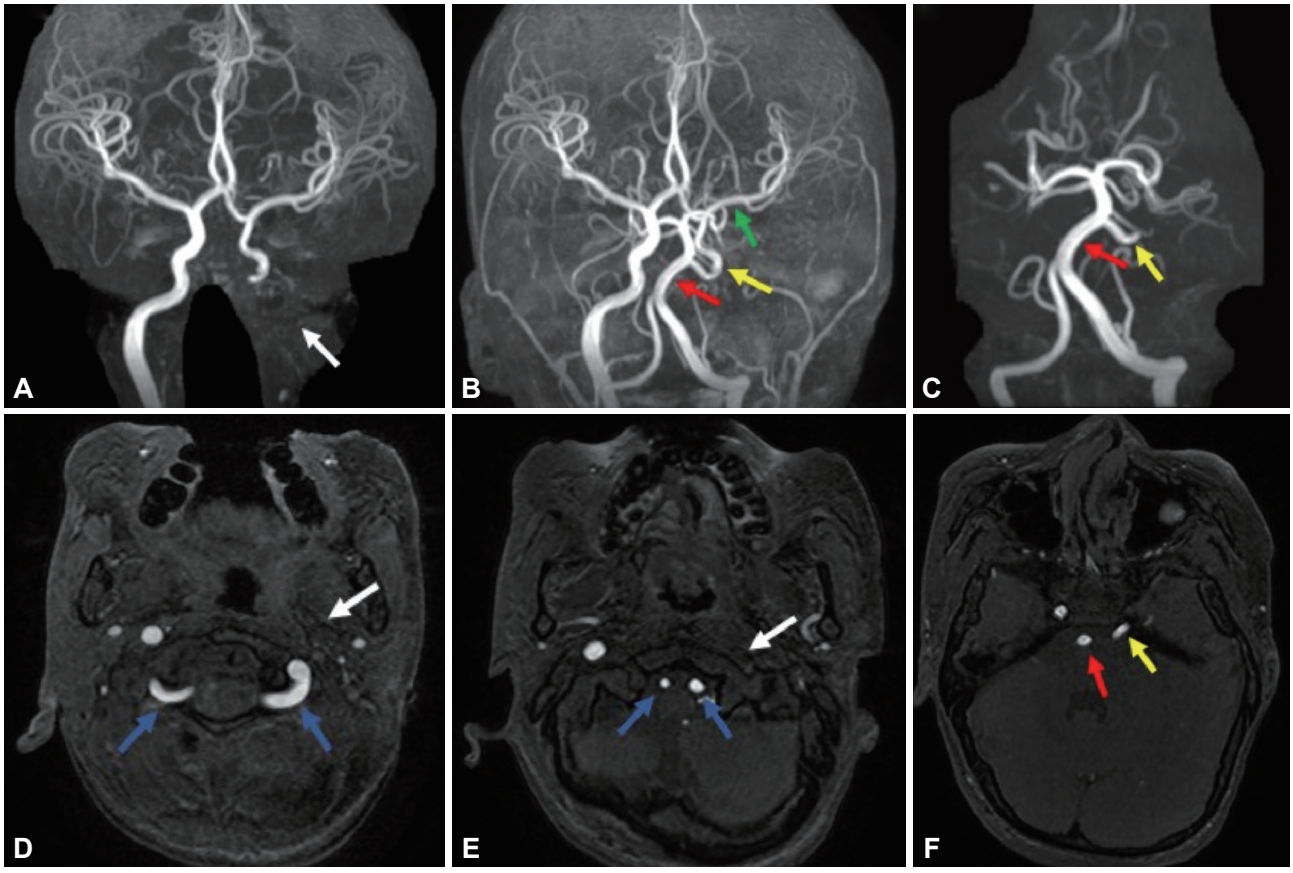

Fig. 1. MRA findings of the persistent trigeminal subtype of ICA agenesis. A: Absent left ICA in MRA (arrow). B: Persistent trigeminal artery (yellow arrow) branching from the basilar artery (red arrow) and connecting to the left middle cerebral artery (green arrow). C: Posterior aspect. Persistent trigeminal artery (yellow arrow) branching from the basilar artery (red arrow). D and E: Absent left ICA (white arrows) with the vertebral arteries evident (blue arrows). F: Axial plane. Persistent trigeminal artery (yellow arrow) branching from the basilar artery (red arrow). ICA, internal carotid artery; MRA, magnetic resonance angiography.

from 0.1% to 0.6% in the general population, but Siddiqui et al.[9] reported that it appears in approximately 50% of patients with CHARGE syndrome, which makes persistent trigeminal artery a potentially important phenotype in that condition. Cerebral vascular anomaly has been evaluated less extensively than cardiac defects during the diagnosis and management of CHARGE syndrome. The possibility of a cerebral vascular anomaly should be considered in patients diagnosed with CHARGE syndrome, and potential neurological symptoms caused by cerebral vascular anomalies should be assessed. Additionally, features such as ICA agenesis may be closely related to aorta and cardiac defects. The present case provides insight into the phenotypic spectrum of CHARGE syndrome and may contribute to the understanding of the genotype–phenotype correlation of pathogenic variants of *CHD7*.[2,8]

Ethics Statement

We confirm that we have read the journal's policy on ethical publication and affirm that this report conforms to those guidelines. This study was conducted in accordance with the tenets of the Declaration of Helsinki and the recommendations of the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine (Seoul, Korea; approval number: 3-2022-0121). Written informed consent was obtained from the patients or guardians, as applicable.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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